SKIN MANIFESTATIONS OF INTERNAL DISORDERS

SKIN MANIFESTATIONS
of
INTERNAL DISORDERS
(DERMADROMES)

By

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WITH 386 TEXT ILLUSTRATIONS
AND 6 COLOR PLATES

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Dedicated

to

My Wife

Marie Wiener M D

PREFACE

Physicians have always been intrigued by the skin manifestations of internal disorders. An early diagnosis of diabetes from the inconspicuous tan of carotenemia, the estimation of the date of a heart attack from the position of the cross furrows on the fingernails, the suggestion of Addison's disease by the pigmented palmar creases of a patient who has no other complaint than fatigue, the intimation of pregnancy of a young woman who wants the little skin tags removed which suddenly appeared on her neck—these and other diagnostic feats have been a constant source of professional satisfaction.

Before the advent of modern diagnostic methods the clinicians probably knew better how to read diagnosis and prognosis from the skin than the present generation which is accustomed to trust objective laboratory methods more than observation. It would be utterly ridiculous to minimize the progress of medicine and to long for the good old times when the doctor, his chin on the golden head of his cane, sat at the patient's bed and watched the degrees of pallor or cyanosis or the intricacies of a rash. And yet it seems that the tremendous wealth of clinical observations on cutaneous phenomena accompanying internal disease has in our time not found the attention it deserves. The observations are scattered mostly throughout the internistic literature and often the descriptions have been given by men without dermatologic training. The dermatologic literature which during the last thirty years has shown an increasing consciousness of the systemic relationship of the skin naturally is more concerned with the internistic background of the dermatoses and much less with the skin manifestations of internal diseases. Thus, there is sufficient justification for a survey and presentation of our knowledge in this field despite the fact that many articles and a few books have been written on the subject. The articles usually deal with but a few of the well known skin manifestations, such as the diabetic dermatoses or the pigmentations in Addison's disease. Only a few papers comprise several or many groups of the internal disorders, among the important being those of Joseph Jadassohn,[1] Bruno Bloch,[2,3] Weidman,[4] U. Wile,[5] Wise and Wolf,[6] Lutz,[7,8] and Bertha Ottenstein.[9] Remarkably few books have been written on the subject. Bulkley[10] published a small volume which contains many valuable observations and in spite of its disregard for the literature

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[1] Jadassohn, J. Hautaffektionen bei Stoffwechselanomalien, 5. Internat. Dermat. Kongr. Berlin, 1904, Berlin, 1905, A. Hirschwald.

[2] Bloch, B. Haut und Stoffwechsel, Verhandl. d. Gesellsch. f. Verdauungskrankh., 1925.

[3] Bloch, B. Einiges über die Beziehungen der Haut zum Gesamtorganismus, Klin. Wchnschr. 1: 153-156, 1922.

[4] Weidman, F. D. Dermatologic Expressions of Internal Medical Diseases, California & West. Med. 33: 666, 1930.

[5] Wile, U. J. Cutaneous Manifestations of Systemic Disease, Ann. Int. Med. 5: 1103-1112, 1932.

[6] Wise, F. and Wolf, J. Skin Diseases in Their Relation to Disturbances of Other Organs, J. Michigan M. Soc. 36: 437, 1937.

[7] Lutz, W. Hautkrankheiten und Gesamtorganismus II, Dermatologica 79: 46-111, 1939.

[8] Lutz, W. Vorwiegend konstitutionell bedingte Dermatosen, Dermatologica 81: 132, 1940.

[9] Ottenstein, B. Hautkrankheiten und Gesamtorganismus, Dermatologica 87: 41-64, 1943.

[10] Bulkley, L. The Relations of Diseases of the Skin to Internal Disorders, New York, 1906, Rebman Co.

and its lack of pictures makes still interesting reading Later attempts included the books of J K. Mayr[11] W Lutz[12] and the compendious monograph by S Jessner and Lutz[13] Of course a large number of monographs deals with parts of the subject. Endocrinology and the skin has been dealt with in treatises by J Strandberg and in a very fascinating way by Mussio Fournier Piaggio Blanco and Cervino[14] Lately E Urbach[4] has given a brilliant presentation of the relationship of skin diseases to metabolism and nutrition a field to which he already had made so many original contributions However *a recent systematic presentation of the skin manifestations of internal disorders does not exist* and the author hopes to fill this gap with the present book.

While preparing this book the author became aware of the fact that the term skin manifestations of internal disorders is not only lengthy but does not cover all the dermatoses which may be part of a syndrome The term skin manifestation implies the existence of something which manifests itself on the skin thus it is perfectly correct to say that the typhoid fever infection manifests itself on the skin with the rose spots However there are dermatoses which accompany diseases of other organs with some regularity without being more than an accompaniment at least to our present knowledge Pseudoxanthoma elasticum for example is often associated with angioid streaks of the retina. We do not know what manifests itself in the phenomenon of pseudoxanthoma elasticum but we know that this dermatosis is the skin part of a syndrome known as Gröenblad Strandberg syndrome It was felt that there is need for a short word expressing precisely and noncommitally such a relationship The word *dermadrome* (literally fellow traveler on the skin) which means the skin part of a syndrome was therefore coined and used throughout this book not only for accompaniments but also as a synonym for true skin manifestations of internal disorders

Within reasonable limits the author has tried to cover the field which the title of the book indicates He has however abstained from forcing into a chapter such subjects which represent entire divisions of medicine as syphilis though it cannot be denied that the syphilitic dermatoses are an outstanding example of the dermatoses of a systemic infection The skin manifestations of allergy and the nutritional disturbances in infancy have not been included partly for the same reason and partly because excellent modern monographs on these subjects are available Some gaps in the presentation of the field may have been caused by the disruption of the supply of foreign medical periodicals during the war and also by the difficulty of obtaining those articles which appeared in the less well-known languages or in remote countries If the original article could not be consulted abstracts were used if possible Most of these abstracts are contained in the Zentralblatt für Haut und Geschlechtskrankheiten

[11] Mayr J K Die Erscheinungen an der Haut bei inneren Krankheiten einschliesslich der durch Behandlung bedingten Schädigungen, Leipzig, 1936 F C W Vogel

[12] Lutz W Stoffwechsel und Haut Handb d H u. Gk 8 252-383 1930

[13] Jessner S and Lutz, W Hautveränderungen bei inneren Krankheiten Handb. d H Gk 4 440-480 1933.

[14] Strandberg, J Haut und innere Sekretion, Handb d H Gk. 8 106-252 1930

[15] Mussio Fournier J C Piaggio Blanco R A and Cervino J M Piel y anexos y glándulas endocrinas, Buenos Aires, 1944, Salva Editores.

relatively few in The Journal of the American Medical Association the Yearbooks of Dermatology the Archives of Dermatology and Syphilology the Archives of Internal Medicine and some other periodicals. The use of abstracts from the Zentralblatt has in most cases been indicated in the bibliography by the addition of Zbl with the numbers of the volume and the page Since these are mostly articles which are difficult to obtain it was thought that this addition might facilitate further research.

The author hopes that his book will be read or consulted by dermatologists as well as by internists and general practitioners. This expectation necessitated that facts which may seem trivial and superfluous to one group of the prospective readers require discussion for the sake of another group Therefore the author asks for indulgence for the introductions to such topics as scarlet fever leukemia gout and other diseases which are more familiar to the internist than to the dermatologist.

The system of bibliography here used has abandoned the usual listing of the references at the end of the chapters or at the end of the book. The author felt that the titles of the sources and the names of the authors who have made the observations should not be hidden away but shown on the same page where their work is mentioned This was done not only as a matter of fairness to the authors but also to induce the reader to look up some of the original sources himself This system of references on the same page with consecutive numbering which had been used for a long time in the periodical publications of the American Medical Association has recently been adapted to medical books.[H]

A glance at the table of contents shows that the book does not primarily deal with the internistic background of skin diseases. However occasional remarks and short paragraphs on this subject have been included if it seemed warranted

With this book, the author wants to strengthen the idea of the unity of medicine. It does not seem unnecessary to work for this idea in order to help to prevent that the medical specialties grow away from each other and lose sight of other fields and of the system as a whole. Nature is neither husk nor kernel she is all in one

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[H] Urbach, E Skin Diseases Nutrition and Metabolism New York 1946 Grune & Stratton, Inc.

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ABREVIATIONS

Zbl after title means that the bstract i the Zentralblatt für H ut und Geschlechtskrankheiten has been used.

Handb. d. H u. Gk. stands for Handbuch der Haut und Geschlechtskrankheiten, herausgegeben von Joseph Jadassohn, Berlin, Julius Springer

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INTRODUCTION

Skin manifestations of a disease of another organ or an organ system may be *specific* or *nonspecific*

Specific dermadromes contain the same pathological elements which cause or characterize the lesions of the disease in another part of the body system Skin metastases of a malignant tumor of the stomach repeat the adenomatous structure of the primary growth Leukemic infiltrations of the skin consist of the typical leukocytes of the leukemia and hematogenous tuberculosis of the skin is still as much tuberculosis as it was in the tubercular focus from which it descended.

Much more frequently the dermadromes are *nonspecific* Neither anatomy nor course seem to repeat the primary disease. The pruritus in Hodgkin s disease sweating in tuberculosis or in arsenic poisoning are such nonspecific manifestations. They are cutaneous responses to pathologic stimuli and since the means of expression which the skin possesses are limited heterogeneous causes may produce identical skin symptoms. Pruritus, perspiration erythema pigmentation hypertrichosis allergic inflammation keratosis are some words from the language in which the skin answers if it is provoked It follows that a conclusion *as to the underlying condition from a nonspecific symptom like pruritus* alone is not possible. In other words the nonspecific dermadromes are *not diagnostic* they are merely *suggestive* of a diagnosis. They have to be weighed together with other manifestations to make a diagnosis possible Naturally this limits the practical value of the knowledge of the cutaneous symptoms of internal disorders. However the same is true of the symptomatology of all other fields. A diagnosis is usually not based on one specific symptom but rather on a characteristic pattern formed by a *variety* of nonspecific manifestations.

Another fact increases the difficulty Hardly one dermadrome is an *invariable* companion of an internal disorder The melanosis *in Addison s disease* is missing in a considerable percentage of the cases Pruritus commonly encountered in Hodgkin s disease diabetes gout arsenic poisoning may be absent. Even the rash in measles or chicken pox may not appear Jaundice in obstruction of the common duct seems to be one of the few inevitable dermadromes.

Before entering the discussion of the skin manifestations of internal disorders, the reader might well ask which *criteria* permit the assumpton of such a relation ship

There is no doubt about the relation of the specific dermadromes to the internal companions to which they are *subordinated* as is the case in focal infection or *coordinated* as in syphilis. For the investigation of the status of the nonspecific dermadromes the statistic method is the most important one If pruritus is associated with diabetes in a larger percentage than with a normal control

group we are justified in calling pruritus a dermadrome of diabetes. This apparently simple method naturally has all the fallacies connected with statistics. The number of cases must be sufficiently large. The character of the material must be considered. For example, in the case of diabetic pruritus it is important whether the patients are hospitalized or ambulatory, controlled or uncontrolled diabetics, wealthy or poor. The control group must be large and its character should correspond to the probed group of diabetics in age, sex, racial and social make up, etc. It is of greatest importance whether observations have been gathered from records which had been written by another physician or whether they have been collected by the author himself with the purpose of his investigation in mind. Generations of interns may not have paid much attention or at least may not have entered a note on the presence or absence of pruritus or epidermophytosis in the diabetic patients. Then a man becomes interested in the question and he starts to ask patients and to make notes. This may cause the apparent incidence to soar.

If *rare* dermatoses occur in association with relatively rare internal diseases the relationship can be accepted if a few cases only have become known. Examples are the few instances of dermatitis herpetiformis after total parathyroidectomy or cutis verticis gyrata in acromegaly or acanthosis nigricans in visceral carcinoma.

Other criteria of a relationship between a dermatosis and an internal disorder are disappearance of the former following successful treatment of the latter as it occurs in some cases of hypertrichosis of ovarian origin. The close parallelism between the ups and downs of the disease and the skin changes is sometimes a good evidence of a relationship. This can be observed in the dermatoses of the legs which sometimes accompany periods of circulatory decompensation.

Skin Manifestations of Internal Disorders

Chapter I

THE DERMADROMES OF SYSTEMIC INFECTIONS

Hematogenous or Metastatic Infections. Microbids (Bloch [7])

The ectogenous infections of the skin, for example impetigo, erysipelas, and the superficial mycoses, do not belong to the subject of this book. If, however, the micro-organisms travel with the blood stream from an infectious focus in the system to the skin and cause there corresponding manifestations of the infection, the resulting dermatosis is a dermadrome of the systemic infection and requires discussion.

When as far back as 1915 J. Jadassohn* gave this definition of hematogenous skin infection he wisely chose the word corresponding. He was aware of the fact that the hematogenous infections are not identical with the primary lesion. They differ more or less, although a relationship can usually be found. The various hematogenous infectious lesions, the microbids (Bruno Bloch) or the ids, for short, have been shown to have a number of common features. The study of the experimental hematogenous infection of the guinea pig with fungi proved particularly instructive for the understanding of the pathogenesis of the microbids in general.

Experimental Hematogenous Fungus Infection.—Saeves [11] in J. Jadassohn's clinic in Berne, Switzerland, was the first to show that a single intracardial injection of an emulsion of spores of *Achorion quinckeanum* and *Trichophyton gypseum* can produce in the guinea pig several crops of fungi-containing clinically typical skin lesions. These mycotic lesions healed spontaneously after about three weeks. The hematogenous skin infections differed little from primary skin infections. The animals developed a generalized specific skin allergy toward fungi just as they did after ectogenous infection. The hematogenously produced lesions appeared to have a certain predilection for shaved or traumatized [12] sites.

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*The hematogenous infections of the skin have been studied intensively by Joseph Jadassohn and Bruno Bloch and their schools.

[7] Bloch, B. Les microbides cutanés, Arch. dermato-syphilig. Hôp. St. Louis 4: 157-194, 1932.

[11] Saeves, J. Experimentelle Beiträge zur Dermatomykosenlehre, Arch. f. Dermat. u. Syph. 121: 161, 1915.

[12] Kogoj, F. Lokalisationsbestimmung hämatogener Infektionen, Arch. f. Dermat. u. Syph. 160: 232-243, 1930.

M Sulzberger[30] then in Bloch's clinic could show that no actual mycotic granuloma of internal organs could be produced by intracardial injection of *Achorion quinckeanum* in spite of the presence of fungi in the spleen and in other organs. The histologic examination of hematogenous skin lesions demonstrated that the fungi could be found mainly in the stratum corneum and in the hairs not in living tissues[31] leaving no doubt about the *elective localization* or *dermatropism* of certain microbes

Foci—The foci from which the microbes may enter the blood can be found in many organs Streptococcic and staphylococcic foci are known to occur in dental granulomas, in abscessed teeth and in many other organs The lungs and the mediastinal lymph nodes may be the foci for the hematogenous spread of tuberculosis. The skin itself may be the site of primary foci which are able to emit fungi tubercle bacilli and other microbes into the system Trauma inflammation with hyperemia and suppuration (kerion) fever and intercurrent infections like colds or influenza are likely to have an influence on the *mobilization* of microbes from a primary focus X ray treatment of a primary trichophytic lesion and injection of trichophytin are named among the factors which have been seen to provoke trichophytids.[31] The traumatization of gonorrheic infiltrates or tuberculous tissues may cause a crop of hematogenous skin infections. All infectious processes which lead to erosion of blood vessels and lymphatics may lead to metastatic infection Jadassohn[32] stresses the importance of all influences which weaken the systemic resistance. The possibility of a release of bacteria from a silent focus into the blood stream apparently without any of the known causes must be considered

The *presence of microbes in the blood* in cases of microbids has been demonstrated for fungi by M Jessner[33] and others[34] and for tubercle bacilli by Kren and Löwenstein[35] Konrad[36] and others Many similar findings especially of pyogenic bacteria are known

Metastatic Sites.—The experimental fungus infection shows that the microbes do not stay and develop wherever they are deposited by the blood stream. The fungi prefer the keratinized tissue other microbes favor other sites Tuberculids are seen most often on the extremities especially the legs probably due to the tendency to stasis in the extremities. Some epidermophytids have a special tendency to form eczematoid epidermophytids in the palm. Traumatized or inflamed areas attract fungi spirochetes pyogenic bacteria or

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[30] Sulzberger M Pathogenesis of Trichophytids The Spontaneous Passage of Formed Elements From the Primary Lesion I to the Circulating Blood, Arch. Dermat & Syph 18 891-901 1928

[31] Bloch, B. Allgemeine und experimentelle Biologie der Dermatomykosen, Handb. d. H Gk. 11: 300-377 1928

[32] Jadassohn, J Importance of Immune Biologic Processes in Morphology of Skin Lesions, Arch. Dermat. & Syph 21 345 1930

[33] Jessner M Trichophytid Zbl. 11 449 1924

[34] Bloch, B Die Trichophytide Handb. d. H. Gk. 11 464, 1928

[35] Kren, O and Löwenstein, E Die Bedeutung der Bazillämie bei den verschiedenen Formen der Hauttuberkulose und bei Lupus erythematodes, Arch. f. Dermat u. Syph 166 375-380, 1932

[36] Konrad, J Demonstration of Tubercle Bacilli in Circulating Blood (Löwenstein Method) Dermat. Ztschr 66 90-37 1933

tubercle bacilli. The appearing of syphilitic papules in areas of friction and maceration is well known [9,19,37]



Fig. 1—Trichophytid (Courtesy Division of Dermatology, Department of Medicine, University of Chicago.)

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*Jadassohn, W. Tierexperimentelle Untersuchungen über hämatogene traumatisch bedingte Hauttuberkulose Arch. f. Dermat. u. Syph. 160: 324-333, 1930.

Common sites of microbic deposits are the vascular nets which surround the *hair follicles*. Hematogenous follicular rashes (lichens) are well known in my coses syphilis tuberculosis and other diseases. J. Jadassohn[26] *suggested that* the fungi in the blood stream like to settle in the follicles because of the close relation to the hair their preferred medium. Microbic metastases in the capillary loops of the *papillae* may cause scarlatiniform rashes roseola, or papules. Those in the *subcutis* produce nodules of all sizes. The *larger blood vessels* especially in the subcutis are another target. Thus reticulated livedo racemosa like forms may ensue as is occasionally seen in syphilis. The *veins* may be the origin of deep nodules in late syphilis. J. Jadassohn[26] felt that these infections originating in the walls of veins (Wolters[27]) do not stem directly from the blood in the veins but rather from the blood in the *vasa vasorum*. Thus the point of attack contributes to shape the clinical pictures of which lichenoid follicular rashes roseola and erythema nodosum are the main representatives.

Other Characteristics of Hematogenous Skin Infection.—Perhaps even more important than the site of the microbic metastasis is the *allergic response* of the skin. Almost always some allergy has already developed when from the primary focus of infection microbes are disseminated through the circulation. The specific skin reactions are mostly positive. Bloch[1] and other authors have seen fresh crops follow injections of specific allergens. The allergic reactions in hematogenous skin infections may though frequently strong be weak or negative as suggested by the so-called anergic tuberculids. In other instances of weak allergy the metastatic lesion shows features of a primary infection that is, greater abundance of microbes and nonspecific inflammation. Miliary tuberculosis and early syphilis are examples. As the immune biologic reaction grows in strength fewer germs and increasingly tuberculoid histologic structures will be found. This is the case in tuberculosis lichenoides, in tuberculoid leprosy in leishmaniasis, and especially in the late stages of syphilis. Syphilids are rich in spirochetes when the luetin allergy is lacking and poor when it is present.[22] Not only the skin may have changed its specific reaction since there are many indications that the microbe itself may have become allergic in the course of its contact with the host. For instance spirochetes and other protozoa may become resistant to previously effective drugs.

General *septic symptoms* like malaise chills and fever and swelling of the lymphatic nodes and joints may accompany the crops.

The general course of hematogenous infectious skin eruptions is usually benign. There is a marked tendency to spontaneous involution as is the case in some tuberculids.

The *distribution* of hematogenous infectious dermatoses exhibits some characteristic features. One would expect that microbes which invade the blood stream especially the pulmonary veins and the large arteries, would land in fairly even distribution in the entire skin. This is not always the case. Syphilitic

[26] Jadassohn, J. Hematogenous Infectious Diseases of the Skin, Arch. Dermat. & Syph. 21 526–538, 1930.
[27] Wolters, M. Lupus nodularis hämatogenen Ursprungs, Arch. f. Dermat. u. Syph. 69 33, 1904.

roseola the acute exanthems, and other blood borne infections, in spite of the great number of individual lesions show modifications in their distribution caused by peculiarities of the terrain. Other examples of uneven dissemination are the circumoral pallor in scarlet fever the predilection of the upper half of the body in variola and varicella the often exclusive localization of papulonecrotic tuberculids on the extremities and of some trichophytids on the palms. Of course symmetric dissemination and the appearance in crops as seen in secondary syphilids or in acute exanthems suggest hematogenous infection but asymmetry does not rule it out. The sarcoids and tertiary syphilis are usually asymmetric. Paucity of microbes in the blood stream or paucity of those germs which can succeed in setting up a hematogenous skin infection may explain the lack of symmetry

Pyogenic Focal Infection.—The hematogenous skin infections from streptococcic or staphylococcic foci particularly in the teeth and tonsils have so far not found the same interest among dermatologists as the corresponding manifestations in the other organs among other specialists. It appears that there exist two groups of investigators who do not seem to know much of each other the dermatologists with the microbids on one side and the proponents of the classical focal infection on the other The former frequently show a skeptical attitude toward the achievements of the latter who in turn often ignore the work of dermatology in this field

Both schools struggled with the question of whether toxic products of microbes are able to produce specific dermadromes or whether hematogenous infection with living germs is a necessary prerequisite.

Today the importance of the question has diminished since it is known that toxins from microbes may produce lesions similar to those of living bacteria and that absence of microbes in microscopic and cultural tests does not prove that the questioned lesions are not caused by germs. J Jadassohn[22] emphasized on several occasions the clinical similarities of many hematogenous toxic and hematogenous infectious dermatoses. Purpura is an example of a dermadrome common in infection as well as in poisonings.

From the pathogenesis of the tuberculids and trichophytids which are more often infectious than toxic, and also from other observations we may conclude that the secondary foci are likely to be of a bacteremic and metastatic nature although bacteria are rarely found in the secondary skin lesions.

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*The best comprehensive review of the field of focal infection by Gutzeit and Parade[21] (1939) with bibliography of about 1,200 items, does not mention the names of J Jadassohn, B. Bloch, nor those of their pupils And this in spite of the fact that most of these authors worked for a long time in the same block in the University Hospital in Breslau, Germany

[21]Gutzeit, K and Parade G W Focal Infect., Ergebn. d inn Med u Kinderh 57 613-722 1939

[22]Jadassohn J Hämatogene Derm tosen Klin Wchnschr 10: 602, 1931

The conception of focal infection is based on the work of Pässler [32] Hunter [33] Billings [34] and particularly Rosenow [35] but the older literature also contains much material pointing in the same direction The term *focal infection* (focus of infection) was coined by Billings [34] who defined it as a circumscribed area infected with pathogenic microorganisms and usually communicating with a mucous or cutaneous surface causing secondary foci through various ways especially through the blood stream Later the definition became more precise. Focal infection may now be defined as a *disease caused by a chronic focus of infection which harbors pathogenic microorganisms and though often dormant itself continuously or continually causes remote symptoms* (modified after Gutzeit and Parade) [35] The teeth and the tonsils are the main sites of the primary foci [36] followed in frequency by the paranasal sinuses the middle ear the bronchi the uterus and



Fig 2 —Focal infection. Sudden and often recurrent crops of acute circumscribed erythema of the cheek Attacks ceased entirely after extirpation of chronically infected appendix

adnexa the prostate the intestinal tract and some other less common sites like varicous ulcers and bronchiectases Rosenow [37] to give an example found tonsillary foci in 51 per cent of his patients with arthritis and in 74 per cent of those designated as having infective lesions of the skin In the latter group 77 per cent had infected teeth

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[32] Pässler H Ueber die Beziehungen einiger septischer Krankheitszustände zu chronischen Infektionen der Mundhöhle Verhandl d deutsch. Gesellsch. f inn Med 26 Kongr p 321 1909

[33] Hunter W Role of Sepsis and Antisepsis in Medicine Lancet 1 77 1911

[34] Billings, F Focal Infection Lane Medical Lectures, New York 1916, D Appleton & Co.

[35] Rosenow E C Zusammenfassung der Forschungsergebnisse über Fokalinfektion und elektive Lokalisation, Med Klin 27 325, 1931

[36] Rössle R Ueber Fokalinfektion Verhandl d deutsch. Gesellsch f inn Med Kong 42 483-496, 1930.

[37] Rosenow E C Herdinfektion und elektive Lokalisation, Verhandl d deutsch Gesellsch. f. inn. Med. Kong 42: 409 930

The *bacteria* which cause focal infection are predominantly streptococci especially the viridans type although staphylococci *Escherichia coli* gonococci and others also have significance. Billings[34] and Rosenow[35] showed that the streptococci in the living tissue of the primary foci can change their characteristics in various ways There were changes in virulence changes in cultural behavior and even transition into other forms for example from streptococci into pneumococci. The observations on character and extent of such mutations are still controversial, but the majority of the bacteriologists recognize them in principle. The explanations for the emission of bacteria into the circulation in crops have been mentioned in the first half of this chapter The finding of streptococci in the blood[36] is relatively infrequent, and there are many series of observations with entirely negative results. The probability of finding small numbers of bacteria in the blood is small. The paucity of germs in the blood distinguishes focal infection from true sepsis. It is well that Billings[34] changed the misleading term oral sepsis to focal infection

A most controversial subject was and still is Rosenow's[37] theory of the *elective localization* of the microbes especially the streptococci Rosenow[37] who considers the assumption of an elective localization as basic in his work showed in a very large series of controlled experiments that streptococci isolated from primary foci had a surprising tendency to produce lesions in animals which corresponded to the secondary lesions seen in the patients from whom the strain was derived. Thus for example streptococci isolated from teeth and other primary foci in 1,539 cases of ulcers of the stomach and duodenum produced in 65 per cent of the animals which had been infected intravenously comparable stomach or duodenal lesions. Other examples of elective localization are the tendency of green producing streptococci to produce lesions in the cardiac valves and of hemolytic streptococci to localize in the joints. The percentages in which lesions could be produced in the rabbit were mostly around 60 often higher rarely lower Thus in 60 per cent of nine cases of erythema nodosum and of twenty nine cases of herpes zoster comparable skin lesions were produced in the rabbit. These findings were startling The experiments were most expertly executed and the numbers of cases and controls, for example 723 cases of arthritis, 206 cases of ulcerative colitis, were large. One would think that Rosenow's[37] impressive material should have settled the question of elective localization in a positive sense once and forever However while confirmations were forthcoming[38] many investigators among them men who had been trained by Rosenow failed to corroborate his results or obtained smaller percentages.[39] Particular care was taken by Von Albertini and Grumbach[40] These authors could find no definite proof for the existence of an organotropism of the streptococci. They believe that the individual resistance of the animals and not the selective organotropism of the microbes, decides whether a localized abscess or a generalized sepsis will follow the injection of

[38]Haden, R. L., and Jordan, W. H. Multiple Onychia as Manifestation of Focal Infection Arch. Dermat. & Syph. 8 31-38, 1923

[39]Azzi, Azzo Focal Infection, Schweiz. med. Wchnschr. 71 1365-1368, 1941

[40]Von Albertini, A. and Grumbach, A. Focal Infection, Schweiz. med. Wchnschr. 68 1309 1938.

cultures. The authors emphasize the fallacies resulting from comparing secondary lesions in an animal which had not been infected before and which receives a single massive dose of bacteria with secondary infection in man where the dissemination of microbes probably occurs continually and allergy has had a chance to develop Von Albertini and Grumbach s[48] experiments did not deal with skin diseases The role of specific *allergy* in streptococcal infections has been demonstrated and emphasized by many observers. In proper concentration skin tests with autogenous vaccine can be made and therapeutic effects reached. Humoral antibodies have been demonstrated However agglutination precipitation and other tests with hyperimmune sera which had proved of great value in Rosenow s hands have not been found suitable by other authors because of the pronounced tendency of the streptococci to spontaneous agglutination [49] Intercurrent infections climate, menstruation nutrition endocrine and other factors may also modify the allergic reactions.

Diagnosis —Many authors stress the importance of a history of frequent colds recurring tonsillitis [52] postnasal dripping occasional stiff neck, myositis arthritis, transitory tenderness in various joints neuritis, endocarditis appendectomy and other episodes of pyogenic infections. Of course the history only suggests focal infection and it constitutes good grounds for a careful investigation [49]

The collaboration of dentists rhinologists and radiologists is often needed Specimens for culture should be taken from the depth not from the surface This is especially important with regard to the tonsils and the teeth The most suitable medium for cultures seems to be Rosenow s brain broth From the isolated strains, a vaccine may be made and intracutaneous skin tests done. These tests are difficult to interpret and controls are necessary Various laboratory methods to demonstrate humoral antibodies are used by some authors but they have not gained general acceptance The demonstration of an infectious focus does not prove that the dermatosis in question is caused by the focus.

The hematologic methods as well as exact thermometry may give hints with regard to the existence of an infection Gutzeit and Küchlin[53] determine the blood sedimentation rate and expose the area suspected of an active focus to ultra short waves An exposure of seven minutes is used for teeth and twelve minutes for the tonsils. An increase of the sedimentation rate two to four hours after the provocation is supposed to indicate activity of the focus in question The patient should be fasting The value of the method is still controversial since other authors obtained similar reactions from normal teeth The advantage of the test is that it is based on the objective phenomenon of the sedimentation rate and not on more or less vague exacerbations of pain or other sensations It seems that no absolutely reliable test for the activity of a focus has been devised

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Ayres, S J and Anderson, N P Focal Infection in Dermatology Arch Dermat. & Syph. 34 421-431 1936

[53]Gutzeit K and Küchlin, W Beitrag zur dentalen Infektion und ein neuer Weg in ihrer Diagnosestellung durch Kurzwellenprovokation, München med. Wchnschr 84 961-965 1937

Treatment.—So far the best evidence to prove the causal relationship between a lesion in the skin (or elsewhere) and a focus of infection is the therapeutic effect of the elimination of the alleged focus. But even here great skepticism is necessary to prevent post hoc, ergo propter hoc conclusions since many of the conditions in question, for example, rosacea, eczema and lichen planus, take an irregular course with frequent remissions and exacerbations. *Penicillin* and the sulfonamides are the first drugs to be tried. The eradication of dental, tonsillar and other foci by surgical means should be attempted. The removal of one accessible focus does not rule out the existence of other inaccessible or undetected foci. Some foci, like endocarditic or aortic granulations, are beyond the surgical reach or would involve formidable operations which are not warranted. Conservative topical methods include local disinfectant and cleansing procedures like swabbing and gargling, but they will hardly influence encapsulated foci in the depths of tonsillary crypts. The treatment with autovaccine from the recovered strains should be tried, but many authors are skeptical. Ayres, Jr., and Anderson[illegible] recommend gradually increasing intravenous injections of the vaccine. Nonspecific protein injections may be tried cautiously but there is some danger of producing reactions in hyperergic patients. General procedures like the salt free diet of Gerson, Sauerbruch and Hermannsdorfer, hydrotherapy and ultraviolet light have been recommended. Acute exacerbations following such apparently harmless treatments as mud baths are known. Severe exacerbations have been observed occasionally after surgical treatment of foci, for example, arthritic exacerbation following extraction of infected teeth or new crops of gonorrheic keratoses after dilatation of a urethral stricture.[illegible] Ayres, Jr., and Anderson[illegible] give a long list of dermatoses suspected to be caused by focal infection. Most of the alleged conditions bear remarks like "some cases" or "occasionally," intimating how little solid ground the imposing work has yielded for dermatology. In the following list which is in part after Ayres, Jr., and Anderson[illegible] the dermatoses are grouped according to the validity of the arguments claiming focal infection in their pathogenesis.

GROUP I

The nature of the dermatosis as a hematogenous infection or toxic manifestation is well established in:

Syphilis
Leprosy
Tuberculosis
Acute exanthems
Septic pyemids
Erythema nodosum
Trichophytids and other mycoids, for example, in blastomycosis
Tularemia
Keratoderma blennorrhagicum
Typhoid fever
Acute exanthematous diseases and many other rashes in infections

[illegible] Brewster, M.: Relationship of Arthritis to Oral Diagnosis, Defocalization and Streptococcus Vaccine Therapy, Am. J. Orthodontics 27: 140-154, 1941.

GROUP II

Focal infection has been shown or suggested with more or less good reasons in some cases of:

Acne rosacea[44,45]
Herpes zoster[51,52,53]
Erythema elevatum diutinum[46]
Lupus erythematosus acutus disseminatus[47]
Generalized telangiectasis[48,49]
Acrodermatitis continua[50]
Angioneurotic edema and urticaria[52]
Alopecia areata[45]
Acne vulgaris (some cases of severe involvement)[52,53]
Dermatitis herpetiformis[53,54]
Pemphigus[54]
Nonmycotic vesicular eruptions of the hands and feet
Purpura
Sycosis vulgaris
Eczema[52,55,56,57]
Dyshydrosis[58]
Lichen chronicus simplex[58]
Chronic paronychia[53]
Pyodermic ulcerations in chronic ulcerative colitis[59]
Erythemas of various kinds[45]
Lichen planus[60]

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[44] Feit, H, Laszlo, E A, and Vero, F Rosacea as Bacterid From Focal Infection, J.A.M.A. 105 1738, 1935.
[45] Barber, H W Dental Infection and Disease of the Skin, Proc. Roy Soc. Med. 20 30-48, 1927
[46] Weidman, F D and Besançon, J H Erythema elevatum diutinum, Arch Dermat. & Syph. 20 593 1929.
[47] Madden, J F Acute Disseminated Lupus Erythematosus, Arch Dermat & Syph 25 854, 1932
[48] Ayres, S J Burrows, L A., and Anderson, N P Generalized Telangiectasis and Sinus Infection, Arch Dermat & Syph 26 56, 1932
[49] Becker, S W Generalized Telangiectasis, Arch Dermat. & Syph 14 387 1926
[50] Barber, H W and Eyre, J W H Acrodermatitis continua (Hallopeau) or Dermatitis Repens (Crocker) Brit J Dermat 39 485 1927
[51] Semon, H C Some Cutaneous Effects of Dental Sepsis, Lancet 202: [illegible] 1922.
[52] Richter, W Focal Infection Dermat Wchnschr 100: 911-915, 1930
[53] Hunstein, W Dentaler Fokus und Hautkrankheiten, Tübingen, Dissertation, 1932
[54] Welsh, H L Specificity of Streptococcus Isolated From Patients With Pemphigus, Arch Dermat & Syph 30 61 1934
[55] Vinber, J W Focal Infections in the Etiology of Eczema, Am J M Sc 170 732-737 1925
[56] Gomes, A A Eczema and Dental Disease Brit M J 2 400, 1926.
[57] Mommsenheimer, A M Fokale Infection und chronisches Ekzem, Arch f. Dermat u. Syph. 157 182-195, 1929
[58] Kämerl, D Ursachen d Dyshidrosen und Ekzeme Dermat. Wchnschr 91 1615-1619 1930
[59] Jankelson, I R and Mazzell, B. F Pyogenic Skin Lesions Accompanying Chronic Ulcerative Colitis, Am J Digest Dis & Nutrition 3 19 1936
[60] Roberts, H L Focal Infection Brit J Dermat 33 310-334, 353-373, 1921

Chapter II

SYSTEMIC INFECTIONS

Pyogenic Septicemia

Bacteremia does not necessarily produce clinical symptoms. If the microbes enter the blood stream in small numbers or only once the natural bactericidal power of the blood often disposes of them quickly as illustrated by postoperative bacteremia. If the blood is repeatedly or constantly fed with microbes from a focus of infection such syndromes as discussed under tuberculosis gonorrhea or focal infection may ensue. The massive presence of bacteria in the blood together with the outstanding clinical symptoms of characteristic fever or wasting is called septicemia or sepsis. If the development of multiple abscesses is an outstanding feature as is often seen in staphylococcic septicemia the term pyemia is often used The term toxemia should be reserved for those conditions which are caused by bacterial toxins such as diphtheria tetanus and botulism

The bacteria causing sepsis in two series of 150 and 255 cases[*] were found to be *Staphylococcus aureus* in 36 5 per cent *Streptococcus hemolyticus* in 36 per cent, and various types of pneumococci in 5.5 per cent The rest of the list predominantly contains other types of staphylococci streptococci and the Friedländer bacillus. In other large series the staphylococcic cases outnumber the streptococcic cases 2 1 or 3 1[*]

Otitis, carbuncles and related conditions are listed (20 per cent)[*] as the most common source of sepsis, others being operation (14 per cent) infections of the genitourinary tract (9 per cent) paranasal sinuses (6 per cent) liver and gall bladder (4 per cent) and miscellaneous (19 per cent) The onset is often sudden occasionally with a severe chill and fever Chills and spiking temperatures occur in about one-half of the cases Sustained low fevers are common and seem to entail a higher mortality[*] Usually the bacteria can be isolated from the blood Endocarditis and metastatic abscesses are the most characteristic complications and causes of death

Hemolysis, hemoglobin staining of the lining of the blood vessels abscesses, particularly of the lungs, reddened and hypertrophic bone marrow cloudy swelling of the kidneys liver and heart and a moderately enlarged and very soft spleen are the ordinary post mortem findings.

Since the introduction of the sulfonamides, the mortality rate has dropped from 67 to 54.5 per cent[*] in staphylococcic septicemia alone from 82 to 74 per cent.[*] The advent of penicillin has probably reduced the mortality still further

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[*]Neuhof H and Arhes, A H Pyogenic Sepsis 255 Cases, Surg Gynec & Obst, 77 444-442 1943

[*]Mendell, T H Staphylococcic Septicemia 26 Cases, Arch Int Med 63 1068-83 1939.

[*]Skinner D and Keefer C S Significance of Bacteremia, Arch. Int Med 68: 851-875, 1941.

Dermadromes.—In contrast to the importance of the skin as a cause the dermadromes of septicemia are neither very common nor important compared with the severity of the general septic syndrome. There seem to be some distinguishing features between the staphylogenic and streptogenic hematogenous skin lesions (pyemids)[64-65]



Fig 3—Acut streptogenic septicemia Universal exanthem of grouped follicular hemorrhagic lesions. Back

Staphylogenic Pyemids.—Pyemids occur in about one third of the cases of staphylogenic sepsis[65 66] They are probably more common than those caused by streptococci.[67] They appear suddenly often with chills and fever heralding a turn for the worse[68] They often start with rashes consisting of macular or urticarial lesions, vesicles umbilicated pustules or bullae[69] The tendency to epidermolysis is considered by some authors a characteristic but inconstant[64] feature of staphylogenic pyemids[7] Petechiae are seldom absent[70] Metastatic subcutaneous nodules and abscesses in varying sizes and depths may especially in infants give the impression of furunculosis.[71] Mendell[72] saw metastatic ab-

[64]Fuchs, D Pyämisch Dermatitiden ("Pyämide") Handb d H u Gk 9 2 440-472, 1934
[65]Robinson S Septicemia Eruptions, Urol & Cutan. Rev 41 490-492, 1937
[66]Felsenthal W Ueber Staphylokokkensepsis, 3 f t a d Grenzgeb d 3 ed Chir 42 183-262 1930
[67]Fraenkel E Metastatische Dermatosen bei akuten bakteriellen Allgemeinerkrankungen Arch. f Dermat u Syph 129 390-403 1920
[68]George P and Olivier H À propos des faits non eaux de staphylococcémies, Presse méd. 34 611 1926
[69]Strandberg J Ein Fall von exkopustulösem Pyämid, Arch f Dermat u Syph. 111 83 1910
[70]Dale T B Septicemia, Practitioner 147 545-557 1941
[71]Finger E Dermatitis p aemica, Wien klin Wchnschr 9 543-548 1896.

scesses in the skin occur in 30 per cent of thirty five cases of staphylogenic septicemia. Nodules which do not form abscesses may resemble erythema nodosum[72] (McCrea after M Barber[72])



Fig 4 —Female Acute st phylogenic septicemia after furuncle. Erythema and scaling.



Fig 5 Acute staph logenic septicemia Ery hema ous eruption

Erythemas of varying hape and extent sometimes clinically identical with true scarlet fever somet mes oseolar or exudativmult form[73] (Bloemen and Scalongne[73]) but he papules vesicles pustules nodules and petechia may be seen simultaneously Ulcerations a e rare

[72]Barber H W Oral Infection and Diseases of he Skin Guy Hosp Rep 77 137 140 1927
Barber M Staphylococcus Albus Septicemia, Brit M J 1 407-408 942

[73]Dohmen A Scarlatiniform Exan hems in Infections With Staphylococcus Aureus Hemolyticus Klin Wchnschr 17 1849- 49 1938

Bloemen, J J and Scalongne H W Metastatische staphylogene Dermatosen Dermat Wchnschr 110: 477-4 2 940

The histologic findings are in line with the clinical picture Edema and vesicles of the epidermis miliary abscesses and papillary capillaries stuffed with cocci and surrounded by leukocytes are the dominant features.

Streptogenic Pyemids.—Pyemids are reported to occur earlier in the course of streptogenic septicemia than the corresponding staphylogenic eruptions. They also often start as macular sometimes morbilliform or scarlatiniform exanthems sometimes as less numerous or solitary erysipeloid patches[77] (Werther and others after Fuchs[84]) Papular and papulopustular[78] or bullous eruptions[76] are not rare. Most authors emphasize the hemorrhagic tendency of the streptogenic eruptions. Petechiae especially on the lower legs, on the buccal mucosa and on other sites are common. They may become vesicular or bullous. In the mouth small yellow specks may be seen on the petechiae [76] Erythema nodosum [77] erythema multi forme [88] and local gangrene and ulceration have been described although the tendency to suppuration is much less pronounced than in staphylogenic lesions Microscopic examination reveals dense streptococcic emboli in the small vessels particularly in the vasa vasorum [78] surrounded by leukocytic infiltrations. The damage to the vascular wall is demonstrated by the extravasation of red cells together with cocci.

Sabouraud (Kitchevatz[78]) is reported to have postulated a staphylo-streptogenic dermatosis analogous to the trichophytids and epidermophytids Of course he meant a hematogenous infection originating from a pyoderma and not from septicemia which in his days was already well known A lichen pyodermicus, after widespread pyoderma formed by acuminate micropapules[79] and resembling lichen trichophyticus or lichen scrophulosorum and also other benign pyodermids have been described under various names although general recog nition is still lacking

It is true that within certain limits the various microbids resemble each other M Favre[80] observed in patients with furuncles and impetigo lichenoid lesions and squamous seborrhoic plaques sometimes resembling pityriasis rosea The author saw in a case of acute pustular acne vulgaris superficial pink lesions which at their edges consisted of very small dull papules. These lesions disappeared when the acne eruption quieted down A series of thirty cases of "strepto-staphylotoxids the largest so far was presented by Kitchevatz.[78] He too saw pyodermids after widespread streptodermas or deep ulcerating staphylodermas. The streptopyodermids which often originate from rhagades behind the ear itched more and were about five times as common as the staphylo-pyodermids Kitchevatz[78] saw erythematous spots which resembled syphilitic roseola scarlatiniform or lichenoid rashes vesicular papular and erysipelatous

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[76] Nicolas, J Mout k H and Gaté J Septicopyohémie streptococcique avec éruption pemphigoïde Province méd Paris 24 101 103 1913 abstracted in Derm t Wchnschr 58 131 1914

[77] Silberstein, H and Fischer M Ein Erythema nodosum—ähnliches gutartig verlaufendes Pyämid, Arch f Dermat Syph 149: 207 1925.

[78] Kitchevatz, M. Strepto-staphylococcies cutanées, I tern. Derm Kongr Kopenhagen, 1930.

[79] Schreus, H T and Goehl, K Lichenoide Eruptionen bei Pyodermien (Lichen pyodermicus Bemerkungen über Komplementablenkung im Blut bei Staphylokokken und Trichophytieerkrankungen. Wirkung der Röntgenstrahlen Dermat Ztschr 31 273-281 1920

[80] Favre M Angiodermite pigmentée et purpurique Nouvelle pratique dermatologique Vol V Paris, 1936 Masson & Cie pp 413-430

lesions and erythematous and herpetiform enanthemas. There were also focal reactions and the appearance of new lesions after autogenous vaccines and toxins. This relatively large amount of material has not found much attention. Occasionally benign pyodermids [60] circinary or annular exanthems[60] and acne necrotica, resembling embolic infarctions have been recorded after various primary pyogenic infections. Balog[61] saw primary staphylogenic skin infections followed by disseminated semiglobular later umbilicated papulopustules which appeared in crops and subsided with the cure of the primary focus. The embolic-bacterial character of these benign pyemids could be demonstrated. More corroboration is needed however. The same is true of the claims[62] that various types of eczema among them nummular eczema are secondary pyodermids and that nonmycotic pustular eruptions of the hands and feet are pyodermids.[63]

In the *treatment* of all pyemids penicillin must be tried first.

Subacute Bacterial Endocarditis; Endocarditis Lenta (Jaccoud Osler's Disease)

The streptococcus viridans which is the most common cause of subacute bacterial endocarditis, probably stems from focal infections of the teeth paranasal sinuses and tonsils.[64] The streptococci produce vegetations on the heart valves especially in patients with congenital or rheumatic heart disease. The vegetations cause fever bacteremia myocarditis, glomerulo-nephritis and embolic metastases. There is a great variety of nervous hematologic, and other symptoms. The onset is gradual. After an early nondescript subfebrile stage of increasing malaise the disease develops into a severe illness with many septic complications and ends fatally after several months in over 90 per cent of the cases. A small minority reaches a bacteria free nonactive stage which too terminates fatally from valvular disease and cardiac decompensation.[64] Penicillin in high doses over many weeks seems to be effective.[65]

Dermadromes.—About one-third of the sufferers from subacute bacterial endocarditis are anemic and very pale, and later jaundiced (90 per cent).[66] *Sweating* is an annoying symptom. *Petechiae* well known to occur in other streptococcic infections are common. In an analysis of eighty-eight cases, they were found in the skin in 60 per cent,[66] in the mucosae in 14 per cent, and in the retina in 11 per cent. The petechiae appear in crops and sometimes have pale yellow or necrotic centers.[66] [67] Petechiae under the nails are stretched to

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[60] Bošnjaković, S. Several Forms of Chronic Pyodermia, Liječ. vjes. 64: 201-207 1932. Zbl 43: 432.

[61] Balog, P. Benign Embolic Pyemid, J. Invest. Dermat. 5: 107 1942.

[62] Krzysztalowicz, F. Eczema From Pyogenic Infection, Przegl. dermat. 24: 309-324, 1929 Zbl. 33: 91, 1930.

[63] Andrews, G. C. and Machacek, G. F. Pustular Bacterids of the Hands and Feet, Arch. Dermat. & Syph. 32: 837-847 1935.

[64] Osler, W. and Christian, H. A. Principles and Practice of Medicine ed. 15, New York, 1944, D. Appleton-Century Company Inc.

[65] Fleming, A. Penicillin, Its Practical Application, Philadelphia, 1946, The Blakiston Co.

[66] Middleton, W. S. and Burke, M. Streptococcus Viridans Endocarditis Lenta, Am. J. M. Sc. 198: 301-322, 1939.

[67] Goldberg, F. Dermatosis in Endocarditis, Venerol. 8: 81-83 1931. Zbl. 41: 78.



Fig 6 —Subacute bacterial endocarditis Purpura.

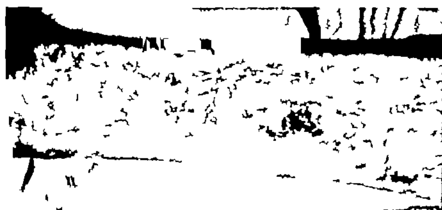


Fig 7 —Subacute bacterial endocarditis. Purpuric rash.

short lines by the growing nail and are often called *splinter hemorrhages* Petechiae about the nails resemble paronychia but they fail to come to a head.[8] If they have central blisters, they resemble erythema multiforme [9] Other varieties of these eruptions have been described as papular or lichenoid [10] maculo-

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[8] Eschbach H Eruption cutanée et endocardit infectieuse prolongée Bull. et mém. Soc. méd d hôp. de Paris 54 297 299 1930

[9] Routier Manifestations cutanées dans l'endocardit lente Zbl. 38 43, 1931

[10] Weissenbach R J Martineau, J and Brisset, J P Manifestations cutanées de la maladie de Jaccoud-Osler Bull Soc franç de dermat et syph 39: 1688-1701 1932

papular and purpuric[n] or subcutaneous and nodular (Osler's nodes) They sometimes prefer the extensor surfaces sometimes the palms and soles (Janeway lesions)

These eruptions heal spontaneously Petechiae on the rectal or sigmoid mucosa are supposed to be an early diagnostic sign in subacute bacterial endocarditis.[n]

Rheumatic Fever

Rheumatic fever[n, n, n] is an infection probably caused by hemolytic streptococci Hereditary and constitutional factors as well as exogenous factors like exposure to cold damp climate and youthful age favor the infection. The outbreak often starts with pharyngitis, tonsillitis and tender joints Chills usher in the fever which is high but does not follow as regular a pattern as in



Fig 8 —Rheumatic nodules

scarlet fever Acute arthritis involving one joint after the other is the center of the clinical picture Endocarditis anemia and more rarely pleurisy iritis chorea and encephalitis may appear While the mortality in the early stages does not exceed 3 per cent,[n] the frequent cardiac damage plays an important part in the mortality in later life

The pathologic findings are characterized by small widespread circumscribed granulomatous nodules which are most often found in the ventricular walls of the heart (Aschoff bodies) and in the walls of many arteries especially of the aorta and the coronary and in the periarticular tissues

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Libman, E and Sacks, B A Hitherto Undescribed Form of Valvular and Mural Endocarditis, Arch Int. Med 33 701 1924

Feinen, J Intestinal Petechiae as Diagnostic Sign in Subacute Endocarditis Internat. Clin 3: 37-47 1941

Leichtentritt, B Acute Articular Rheumatism, in Pfaundler and Schlossmann, Diseases of Children, Vol III Philadelphia, 1934, J B Lippincott Company pp. 253-278

Leichtentritt, B Die rheumatische Infektion im Kindesalter Ergebn. d inn Med Kinderh 37 1-99 1930

Dermadromes —The skin participates in the syndrome in various ways. *Pallor* is common. The skin of the extremities frequently becomes glossy and there may be redness of the palmar eminences. The palms are moist. The repeated *sweating* often causes miliaria, especially on the chest and the inner surfaces of the arms. *Petechiae* and other hemorrhagic signs have often been observed Keil[95] saw them in 10 per cent of 523 cases. Recently[96] it has been demonstrated that children with rheumatic fever generally show a low capillary resistance, especially in late winter and before barometric depressions



Fig. 9 —Cutan-subcutaneous rheumatic nodules about the olecranon.

Urticaria occurs in the early stages.[97] *Erythema nodosum* has often been linked to acute articular rheumatism,[98-101] but the evidence is scant and there is a modern tendency to deny any relationship[99] The observation that such recognized rheumatic diseases as endocarditis and chorea are seldom connected with erythema nodosum has been interpreted as evidence against its rheumatic character[100] (Kassowitz after Leichtentritt[99])

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[95]Keil, H Rheumatic Erythemas, Ann Int Med 11 2246, 1938.

[96]Brown, E E and Wasson V P Capillary Resistance in Rheumatic Children, J Pediat 18: 328-336 1941

[97]Traub Erich Ueber die Bedeutung der *Hauterscheinungen beim akuten Gelenkrheumatismus*, Ztschr f Kinderh 58 709-730 1937

[98]Hadley H G Dermatoses of Rheumatic Fever Urol. & Cutan. Rev 45 713-714, 1941

[99]Keil, H Relation of Erythema Nodosum and Rheumatic Fever Ann I t. Med. 10 1686, 1937

[100]Feer E Zur Aetiologie des Erythema nodosum Schweiz med. Wchnschr 56 643-645 1926

Erythema multiforme[61-64] sometimes appears with exacerbations of the articular disease.

The erythemas in rheumatic fever seem to have been over-classified from a morphological viewpoint. It is sufficient to distinguish between nodular papular and erythematous rheumatic skin manifestations. Transitional forms exist. Keil[60] found 181 eruptions among 523 cases of rheumatic disease. Besides more or less nonspecific dermatoses like hemorrhagic eruptions, telangiectases urticaria scarlatiniform exanthems, in approximately 10 per cent of the cases rheumatic erythemas and in 7 per cent subcutaneous nodules could be found. Erythema nodosum is not included.

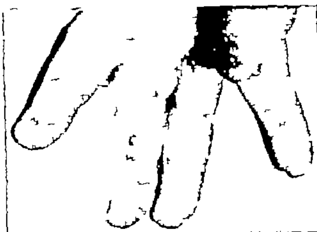


Fig. 10.—Cutaneous rheumatic nodules. (From Rosenberg, W. A. Arch. Dermat., 1934.)

The *rheumatic nodules* (rheumatismus nodosus) appear in crops more often in the subcutaneous tissues than in the cutis itself.[65] They vary from mustard seed to olive size. They are movable nontender and covered with normal skin. They are most often found over the olecranon about the elbow joint, over the knuckles and other bony eminences, for example over the forehead and along the crest of the vertebrae. The nodules are often symmetrically distributed particularly on the limbs. The rheumatic nodules must be regarded as indicating activity of the rheumatic infection which means an unfavorable prognosis.[64-67, 66] Other rheumatic lesions especially rheumatic heart disease are almost always

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[61] Singer, G. Die Hautveränderungen beim akuten Gelenkrheumatismus, nebst Bemerkungen über Erythema multiforme. Wien. klin. Wchnschr. 10: 841-844, 1897.

[62] Müller, Theodor. Ein erythematös-bullös-pustulöses Exanthem bei Polyarthritis acuta, Dermat. Ztschr. 62: [illegible]-274, 1931.

[63] Meyer, August. Akuter Gelenkrheumatismus mit Erythema pustulosum, Ztschr. f. klin. Med. 117: 413-424, 1931.

[64] Rieben, J., Girard, J., and Picard, D. Un cas d'érythème multiforme au cours de la maladie de Bouillaud, Bull. Soc. franç. de dermat. et syph. (Réunion dermat., Nancy) 45: 1760-1763, 1938.

[65] Rosenberg, W. A. Cutaneous Rheumatic Nodules, Arch. Dermat. & Syph. 30: 377-384, 1934.

[66] Struthers, R. R., and Bacal, H. L. Significance of Rheumatic Nodules in Childhood, Canad. M. A. J. 46: 378-381, 1942.

present and the mortality is as high as 31 per cent [107] Recently less pessimistic opinions on the prognostic significance of the rheumatic nodules have been voiced [98] It has even been said that the appearance of rheumatic nodules may indicate the subsiding of the particular rheumatic incident though not of the disease. [98] Histologically they correspond to the Aschoff nodules of the myocardium. Leichtentritt[94] succeeded twice in isolating streptococcus viridans from excised nodules In a third case he and Biberstein[94] found cocci in microscopic sections

The rheumatic nodules must be interpreted as true infectious metastases. The rheumatic nodules usually heal occasionally they may take on the appearance of chronic, hard almond-sized subcutaneous cystic tumors in the neighborhood of the large joints especially the elbow Such nodosities which are well known in other infectious diseases particularly spirochetoses are called juxta articular nodules [109,110,111] H Hoffmann [110] however in his comprehensive monograph on juxta articular nodes does not believe that rheumatic fever plays a part in the etiology of these lesions

Cutaneous rheumatic nodules [94] are much rarer than subcutaneous ones. They have been observed on the fingers and palms as red not painful slightly indistinct papular lesions which do not ulcerate They consist of perivascular infiltration with endothelial proliferation In later stages giant cells develop [112]

Rheumatic papular erythema is a discrete red eruption of small papules mainly but not exclusively about the articulations. Keil[96] found it in 3 per cent of his 523 patients with rheumatic fever Like other rheumatic eruptions it appears in crops. Keil[96] separates erythema marginatum with polycyclic and raised borders from papular erythema Much more significant and better known than the papular eruptions is the flat *annular erythema* [113] which is so characteristic and so intimately connected with rheumatic infection that it can be called a specific rheumatic dermatosis. The incidence given by various authors varies widely Erythema annulare is still considered a rare complication which seldom occurs more frequently than in 10 per cent of children with rheumatic fever [7] (Wallgren after Traub[97]) although Leichtentritt[94] and Lehndorff and Leiner[113] give figures higher than 60 per cent These differences may be largely caused by the type of clinical material because erythema annulare is mainly a dermadrome of rheumatic disease in children with endocarditis The rash starts with pale bluish pink maculae of only a few millimeters in diameter These spots soon blanch in the center and spread peripherally with an active but not infiltrated margin Thus polycyclic or zigzag often rather thin almost linear figures result

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[107] Hayes, R M and Gibson, S Rheumatic Nodules in Children, J.A.M.A. 119 554-555 1942.
[98] McCulloch, H in Discussion of Struthers, R R., and Bacal, H L Rheumatic Infection in Childhood Sedimentation Rate and Schilling Count Am. J Dis Child 51 1061 1936
[109] Hopkins, H H Subcutaneous Nodules of the Juxta-Articular Type Bull Johns Hopkins Hosp 49 5-10 1931
[110] Hoffmann, H Juxtaartikuläre Knoten, Handb d H u Gk. 12, 1 419-498 1932.
[111] Katz, G Juxta-artikuläre Knoten bei Gelenkrheumatismus, Ztschr f klin Med 129 563 1936
[112] Gadrat J Rheumatismal Papulous Erythema Dermal Lesions of Aschoff Kitage Nodule Type Case Bull soc franç d dermat et syph. 44 1782 1784, 1931
[113] Lehndorff H and Leiner O Erythema annulare Ein typisches Exanthem bei Endokarditis, Ztschr f. Kinderh 32 46-53 1922

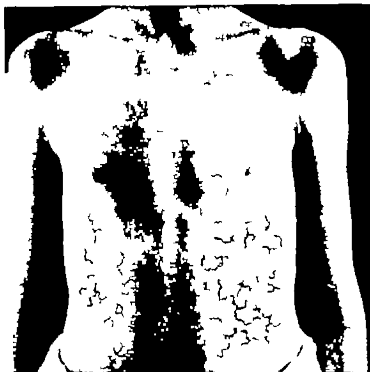


Fig 11 —Erythema annulare rheumaticum. (Courtesy Dr Arthur F Abt.)



Fig 12 —Erythema annulare rheumaticum (Courtesy Dr Erich Urbach.)

The lesions, which appear most often on the chest, less often on the abdomen back, and extensor surfaces of the limbs, are delicate, not infiltrated not scaly not tender and do not itch The erythema has not been observed on the mucous membranes. It appears in one or several crops and the individual crops usually last two to five days.[83]

Since the eruptions may follow each other in short intervals the patient may have erythema for years. The rash may easily be overlooked. Leichtentritt[83] found erythema annulare always connected with rheumatic endocarditis or chorea and he emphasizes its ominbus significance. Other authors do not share his pessimistic interpretation [87,114] but all agree that it has not been seen in endocarditis of nonrheumatic character

The biopsy[115] shows neutrophilic infiltration as a main characteristic. Bacteria have not been found in the lesions. Löwenstein[116] and his group were able to cultivate the tubercle bacillus from the blood of one case of rheumatic fever with erythema annulare. This finding still lacks confirmation. The eruption is now regarded as an expression of cutaneous allergy [117]

Still's disease is a chronic, articular disease of childhood. Fever generalized lymphadenitis and splenic tumor are outstanding features. *Streptococcus viridans* has been demonstrated in the blood by Leichtentritt.[84] Periarticular papules and erythematous eruptions have been reported.[86]

Palindromic rheumatism is a disease characterized by often recurring relatively short attacks of arthritis.[118] Although there is no connection with rheumatic fever intracutaneous and subcutaneous nodules mainly on the fingers have been described in some cases. The nodules were mostly short lived rarely persisting over a long period

Periarteritis Nodosa

Periarteritis nodosa[119] is characterized by multiple inflammatory destructive foci in the walls of the smaller arteries, which may lead to aneurysm and other severe circulatory disturbances The clinical picture varies according to the area which is predominantly involved. Males outnumber females 3 1 [120] Age is not a decisive factor Acute infectious diseases of many kinds have often been observed to precede the outbreak of periarteritis nodosa The onset is usually though not always rapid. Repeated attacks and exacerbations often characterize

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[114] Abt, A. F Erythema Annulare Rheumaticum, Am. J M Sc. 190 824, 1935.

[115] Carol, W L L and Van Krieken, J A Histopathologie des Erythema annulare von Lehndorff und Leiner Acta paediat 17 372, 1935.

[116] Löwenstein, Ernst Die Tuberkelbazillämie in ihrer Auswirkung auf die Gesamtmedizin. Mit einem klinischen Teil von Carl Reitter Wilhelm Neumann und Otto Kren, Leipzig und Wien, 1936, Franz Deuticke

[117] Urbach, E and Bleier A Erythema Annulare Rheumaticum (Lehndorff Leiner) Case Arch. Dermat & Syph. 41 516-520 1940.

[118] Hench, P S and Rosenberg, E F Palindromic Rheumatism, Proc. Staff Meet Mayo Clin. 16 808-815, 1941.

[119] Kussmaul A and Maier R. Ueber eine bisher nicht beschriebene eigenthümliche Arterienerkrankung (Periarteritis nodosa) die mit Morbus Brightii und rapid fortschreitender allgemeiner Muskellähmung einhergeht, Deutsches Arch f klin. Med 1 484 1866.

[120] Harris, A W Lynch, G W and O Hare J P Periarteritis Nodosa, Arch Int. Med. 63 1163-1182, 1939

the course. In more than 90 per cent of the cases, the outcome is fatal after less than one year In a review of 101 pathologically confirmed cases, Harris, Lynch and O Hare[120] listed as significant symptoms and signs fever (80 per cent) leukopenia up to 5 400 (70 per cent) renal manifestations like albuminuria (64 per cent) abdominal pain (27 per cent) cylindruria (46 per cent) hyper tension (64 per cent) edema (52 per cent mostly of cardiac distribution) loss of weight, hematuria, and neuritis. Thoracic pain dyspnea headache and vertigo are common The diagnosis is usually made post mortem However with better knowledge of the dermadromes and greater number of biopsies the disease is being recognized more frequently during life.[120,121,122]

The *cause* of the disease is not known but it has nothing to do with syphilis as was early suggested. It is striking that periarteritis nodosa has so often developed shortly after or even in immediate connection with various infectious diseases especially those caused by hemolytic streptococci While the staphy lococcus, the meningococcus, and the gonococcus are on the list of bacteria which have been found in close association with periarteritis nodosa,[128] the streptococcus is by far the most frequent one. A correlation to rheumatic fever with Aschoff bodies and verrucous endocarditis was discovered in four of Spiegel s[135] seventeen cases and in one of Rothstein and Welt.[123] The clinical course often suggests septicemia. The coincidence with well-established allergic states and also ex perimental evidence of infection[124] suggests allergy as an important pathogenic factor in periarteritis nodosa.[125]

The *treatment* is symptomatic. In one case sulfapyridine together with acetylcholine *seemed to be curative.*[132]

Dermadromes.—Cutaneous manifestations occur in about 25 *per* cent.[133,136] In rare instances almost exclusive involvement of the skin, without participation of the internal organs has been observed.[134-136] The case material permits a tentative grouping[133,136] into nodular erythematous, and hemorrhagic eruptions

The most characteristic element is the periarteritic *nodule* which may be found in or under the skin. These nodules have been noted in roughly 25 per cent of the cases, but they probably often have escaped observation The lesion is very seldom larger than a pea, more often smaller In hemorrhagic cases the nodules may reach the size of a robin s egg[137] or larger and may become cystic and blood filled. The nodules which have been seen to appear in crops in various stages of the disease are hardly ever more than fifty in number In order of frequency they have been observed on the forearm chest, legs, abdomen

[131] Vining, O W Periarteritis Nodosa, Arch Dis Childhood, 13 31-44 1938
[132] Legroa, J Periarteritis Nodosa or Kussmaul-Maier Disease First Case Diagnosed in Infant During Life Recovery From Therapy With Sulfapyridine and Acetylcholine Arch Françaises de Pédiat. Paris, 2: 118 118, 1944-1945.
[133] Ketron, L W and Bernstein J C Cutaneous Manifestations of Periarteritis Nodosa, Arch. Dermat. & Syph 40 929-944 1939
[134] Matras, A Zur kutanen Form der Periarteritis nodosa, Wien klin. Wchnschr 61 901 1938.
[135] Spiegel, R Periarteritis Nodosa, Arch. Int Med. 58 993 1936.
[136] Boyd, L J Periarteritis Nodosa, Cutaneous Symptoms, Bull New York M Coll., Flower & Fifth Ave. Hosps 3: 178-182, 1940.
[137] Alkiewicz, J Multiple nekrotisierende Periarteritis nodosa der Haut mit Acanthosis nigricans, Arch. f Dermat. Syph 168: 822, 1933

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[113] Abe A F Erythema Annulare Rheumaticum Am J M Sc. 190 824, 1935.

[114] Carol, W L L and Van Krieken, J A. Histopathologie des Erythema annulare von Lehndorff und Leiner Acta paediat 17 372 1935.

[115] Löwenstein, Ernst Die Tuberkelbazillämie in ihrer Auswirkung auf die Gesamtmedizin. Mit einem klinischen Teil von Carl Reitter Wilhelm Neumann und Otto Kren, Leipzig und Wien, 1936, Franz Deuticke

[116] Urbach, E and Bleier A Erythema Annulare Rheumaticum (Lehndorff Leiner) Case Arch Dermat & Syph 41 515-520 1940.

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[118] Kussmaul A and Maier R Ueber eine bisher nicht beschriebene eigenthümliche Arterienerkrankung (Periarteritis nodosa) die mit Morbus Brightii und rapid fortschreitender allgemeiner Muskellähmung einhergeht, Deutsches Arch f klin Med. 1 484, 1866.

[119] Harris A W Lynch, C W and O Hare J P Periarteritis Nodosa, Arch. Int. Med. 63 1163-1182, 1939

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[131] Vining, C W Periarteritis Nodosa, Arch. Dis. Childhood, 13 31-44, 1938.

[132] Legrés, J Periarteritis Nodosa or Kussmaul-Maier Disease First Case Diagnosed in Infant During Life Recovery From Therapy With Sulfapyridine and Acetylcholine Arch. Française de Pédiat., Paris, 2 113-118, 1944-1945.

[133] Ketron, L W and Bernstein J C Cutaneous Manifestations of Periarteritis Nodosa, Arch. Dermat. & Syph 40 929-944, 1939.

[134] Matras, A Zur kutanen Form der Periarteritis nodosa, Wien. klin. Wchnschr 51 661, 1938

[135] Spiegel, R. Periarteritis Nodosa, Arch. Int. Med. 58 993 1936.

[136] Boyd, L J Periarteritis Nodosa, Cutaneous Symptoms, Bull. New York M Coll Flower & Fifth Ave Hosps 3 178-182, 1940.

[137] Alikiewicz, J Multiple nekrotisierende Periarteriitis nodosa der Haut mit Aneurysmabildung, Arch f Dermat. u Syph. 168 322 1933.

face back fingers, scalp scrotum and tongue.[124] Sometimes a linear reticular or livedo racemosa like arrangement and pulsation indicate their connection with an artery [123,124,125] This connection can be demonstrated better by capillaroscopy (Weigeldt after Boyd[126]) The lesions are tender even painful and may be slightly raised purplish or red and surrounded by erythematous halos which may coalesce The center may appear grayish and depressed indicating necrotic changes[127] and a scab may appear on superficial nodules. The nodular cases may suggest erythema nodosum.[128] The nodules have a tendency to heal leaving a tan-colored pigmentation Matras believes that the nodular type of periarteritis nodosa takes a more benign course.

The second important cutaneous feature of the disease is *purpura* Petechiae and small purpuric spots, sometimes with a white center [129] are common sometimes abundant Large cutaneous extravasations (apoplexia cutanea)[130,131,132] resembling purpura fulminans have been described by many authors.[127] These hemorrhages may involve entire regions. They may break down and form gangrenous ulcers of varying sizes depth and numbers [71, 131] sometimes climaxing in the mutilation of the acra of the extremities.[131,131] The coagulation time may be prolonged and the fibrinogen reduced to 50 per cent [131]

Besides the most characteristic features the nodules the p[...] gangrene roseola[132] and other erythemas and ephemeral rashes [...]recurring rel[...] tioned Pigmentation though not in the list compiled by Ha[...]tion with rhe[...] O Hare [133] is a feature and may have the characteristics of A[...] on the fingers [...] Periarteritic involvement of the adrenals has in fact been [...]ort lived rarely [...] cases. (Spiegel after Boyd [126] Edema and profuse sweatin[...] night and moderate adenopathy are common symptoms

The *histological* picture is well established It shows infilt[...] walls of small and medium-sized arteries with leukocytes and round[...] destructive cells of the Langhans type are common All layers especially the[...] and other thickened and the elastica and the muscle fibers are destroyed [12] u[...]g to the the proliferation of the intima leads to occlusion thrombosis, and her[...][134] Age Tissue and blood eosinophilia are frequently a conspicuous feature. T[...]n been cutaneous fat is often the site of a patchy necrosis and of an inflammat[...]ually filtration with necroses in spots and numerous monocytes and giant ce[...]erize Extravasations are exceedingly common

[127] Carol W L L and Prakken, J R Periarteritis Nodosa, Acta dermat venereol. 18 103 1937

[128] Goldschlag F and von Chwalibogowski, A Ueber einen Fall von Periarteritis nodosa mit verbreiteten Hauterscheinungen Arch f Dermat u Syph 172 622 1935

[129] Freund F Periarteritis Nodosa, Arch Dermat & Syph 162: 158, 1930

[130] Löhe H and Rosenfeld H Multiple Hautmangrän bei Periarteritis nodosa, Dermat Ztschr 61 299-330 931

[131] Danowich M M Polayes, S H and Charet R Periarteritis Nodosa Ann I t Med 16 1149-1179 1942

[132] Rothstein J L and Welt S Periarteritis Nodosa, Am J Dis Child 45 1277 1933

[133] Rich A R and Gregory J E Periarteritis Nodosa as Manifestation of Hypersensitivity Bull Johns Hopkins Hosp 72: 65 1943

[134] Moschcowitz E Periarteritis Nodosa J Mt Sinai Hosp 5 237-239 1938

Scarlet Fever

Scarlet fever is caused by certain strains of hemolytic streptococci which are found mainly in the discharges of the upper respiratory tract. Contagion occurs predominantly among children from 1 to 5 years of age (rarely in infants) by close contact with patients and possibly though seldom through carriers or media such as milk toys, or pets. The disease is most contagious during the first week. The incubation period is probably two days[134] but the observations vary from one to seven or more days. The onset is sudden with nausea and high temperature. A few convulsions and vomiting are common at this time but chills are uncommon There are regularly early sore throat and a coated tongue. The scarlet fever exanthem appears after twelve to twenty four hours and reaches its height within five days, the patient frequently being very ill The fever gradually falls, the rash fades and peels within three weeks and then recovery is reached unless complications develop These complications include otitis media (14 per cent) arthritis (7 per cent) nephritis (4 per cent) and a number of rarer conditions (Hunt after Dick[135])

The mortality[137] in the United States is between 1 and 2 per cent in some communities much less this rate varies considerably during epidemics and in different countries However approximately 4 000 deaths from scarlet fever occur every year in the United States. Except for the complications the post mortem findings are essentially negative. The diagnosis rests on the clinical picture especially the rash n connection with exposure, an epidemic, and the occurrence of hemolytic streptococci

Dermadromes.—In rare cases, the outbreak of the disease may be preceded a transitory diffuse or spotted rash on the inner thighs.[138] Such *fore-exanthems* cur in other exanthematic infections too Most of the new monographs on arlet fever do not mention this rash

The scarlet fever *exanthem* appears early often during the first day of the isease but occasionally the rash is delayed as much as five days.[137] Diffuse ythema of the palate with red spots[139] marks the appearance of the exanthem. This exanthem is quickly followed by the skin eruption which starting at the eck creeps downward and reaches the feet in two to three days. The face usually remains free but it is flushed from fever Morawetz[139] mentions that the exanthem involves the face. The area around the mouth stays pale with a yellow hue This diffuse and relatively wide circumoral pallor includes the lips and often the chin It is much wider and less sharply limited than the narrow perioral strip which often remains unaffected in various other inflammations and pigmentations about the mouth The rash is often particularly pronounced on the femoral triangles on the abdomen and in the bends of the joints. Here the folds may appear more marked and slightly hemorrhagic (Pastia s lines)

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[135] Dick, G F and Dick, G H Scarlet Fever Chicago, 1938 The Year Book Publishers, Inc.

[137] Toomey J A Scarlet Fever in J Brennemann Practice of Pediatrics, Hagerstown, Md 1944, W F Prior Company Inc

[138] Schlossmann, A and Bottinger A Scarlet Fever in Pfaundler and Schlossmann, The Diseases of Children, Vol III, Philadelphia, 1935 J B Lippincott Company pp. 78-169

[139] Morawetz, G Arz Exantheme Scharlach Handb d H u. Gk, 2? 410-424 1930.

The rash is a bright red erythema in which small punctate splashes can be discerned. On the extremities, the pin point spots are less numerous and therefore better recognizable. These very small points are engorged papillae[141] and follicles.[139,142-143] The swelling of the follicles and a slight infiltration of many of the red points may give a chagreen like impression to the hand. Mottling of the skin may be present on the extremities.[144] In unusual instances the skin is edematous making the rash look like dermatitis. Minute, clear rarely pustular[145] vesicles may be scattered over the red background This phenomenon which is evidence of a more severe inflammation is known as *miliaria scarlatinosa* The vesicles the content of



Fig. 13.—Scarlet fever Rash flushed face, and circumoral pallor on third day (Courtesy Dr Max Fox.)

which is alkaline do not correspond to the sweat glands They may be abundant or even confluent forming large bullae [145] The erythema fades on transient pressure or when the skin is stroked with the fingernail and after ten to twenty seconds a white sometimes slightly icteric dermographism appears. [9] Small numbers of *petechiae* are common especially in the flexures The tourniquet test is usually positive and petechiae can easily be provoked by pinching Edema of the dermis often causes slight puffiness of the face, ears and fingers The

[141] Unna, P G Histopathologie d Hautkrankheiten, Berlin, 1894 A Hirschwald.

[142] Kritch, N Pachine A. and Sidorow P La peau dans la scarlatine Étud histologique Arch. de Méd d enf 32 313-326 1929.

[9] von Bormann, F Scarlet Fever Review of Literature Med. Klin. 37 661-664 1941

[143] Lehmann, W Streptokokkenerkrankungen Ergebn d inn Med. Kinderh. 40: 604 749 1931.

[144] Sobel, N in Mackee G M and Cipollaro A C Skin Diseases in Children, New York, 1946, Paul B. Hoeber Inc

[145] Liebmann G Miliaria scarlatinosa suppurativa, Med Klin. 33 1364, 1937

exanthem reaches its full height during the second half of the first week. It then disappears, often in the same order in which it came. During the period of involution the redness may still be pronounced in the evening although the skin appears pale in the morning. During the second week the skin becomes dry and the *desquamation* starts usually about the neck or on the lips, sometimes at the sides of the face, showing that in these cases the scarlet exanthem had involved the face also. The desquamation is at first branny but in the third week the typical peeling in large flakes develops. The thick horny layers of the epidermis of the hands and feet are the last to go. The desquamation varies according to the intensity of the exanthem. While desquamation of fairly large shreds from the finger tips and toes is common the shedding of glovelike casts is quite rare. The epidermis which is ready to peel usually starts to crack under the toes and then peels off toward the tips as well as toward the soles. After a few days ragged flakes hang around the nails which in rare instances may come off also. It has often been said that the stripping of the shreds proximally from the nails over the digits is an almost diagnostic sign of preceding scarlet fever.



Fig 14 —Scarlet fever. Desquamation.

Usually the exanthem does not itch. However, the period of desquamation may be troubled by pruritus. Some cases of scarlet fever with a mild exanthem but unusually severe pruritus have been reported.[149] In rare cases the rash may fail to develop or may be very light. These cases are contagious and desquamation may or may not follow.

In true relapses of scarlet fever the exanthem may repeat itself[150, 151] however true relapses are exceedingly rare. *Desquamation erythema* or erythema post

[149] Lortat-Jacob L. Le prurit dans la scarlatine. La forme prurigineuse de la scarlatine, Presse méd 2 267-269 1929

[150] Hubrecht, Eberhard. Zur Klinik der Spätexantheme nach Scharlach, Monatschr f Kinderh. 59 1 17 1933

[151] Leiner Carl. Hautveränderungen bei akuten Erkrankungen des Kindesalters, Wien. med. Wchnschr 79: 1130 1929.

scarlatinosum is a dermatosis which is seen in less than 1 per cent [137] during the desquamation period or during relapses In one type there are round or poly gonal red slightly papular spots of fingernail size or smaller which have an accentuated deep red margin and a collar of scales. They cover the lower trunk, the buttocks and the thighs in a much less regular or pronounced pattern than the exanthem.[131] Another variety is a cracked net-shaped erythema and der matitis with desquamation.[147]

Striae cutis distensae are not infrequently seen in adolescent girls after scarlet fever (see striae in chapters on puberty and pregnancy)

Moderate swelling of the superficial *lymphatic nodes* is common during the eruption The nodes under the angles of the the jaws which correspond to the ton sils are often infected These and other neck nodes rarely other lymphatic glands may suppurate and break down

The *oral* manifestations of scarlet fever are of great importance [139] In the initial stage before the exanthem the pharynx is reddened and the tongue coated The diffuse initial redness of the throat soon changes into the enanthem which consists of bright red or hemorrhagic points especially over the soft palate and the anterior pillars The uvula and the hard palate are often left free and rel atively pale The tonsils become swollen early white exudate showing in the lacunae. The exudate may form diphtheroid membranes and necroses which may cover the entire tonsil Ulceronecrotic lesions may even invade the tongue[140] and extend to the pillars and the soft palate

The changing and characteristic appearance of the *tongue* has for more than a century been considered of great diagnostic importance but recently it has lost some of its import since typical scarlatinal glossitis occurs in only one-half of the cases, and may also be found in measles and German measles [139] The first changes in the tongue often precede the exanthem in scarlet fever [141] The early yellowish coating is soon pierced by the swollen red papillae fungiformis, producing the strawberry tongue The edges and the tip of the tongue usually become free early so that a red V-shaped area results.

After about two days the yellow coating vanishes. On the fifth to eighth day the whole tongue is deep red and covered with raised papillae constituting the raspberry tongue [138]

Since the first description by Lister in 1858 (Klan[142]) a great number of cases of acute symmetric *gangrene* of the skin in scarlet fever have become known sometimes under names such as gangrenous purpura purpura fulminans or disseminated skin gangrene

Suddenly sometimes after a mild or moderately severe course of scarlet fever usually in or shortly after the third week but occasionally as late as nine months after the onset [143] patches of gangrene may appear on the skin often in a

[139]Trask, J D Scarlet Fever Chap XXI New York 1940 Oxford University Press

[140]Berger J Ulcero-nekrotische Glossitis bei Scharlach Monatschr f Kinderh 38 [illegible] 1938

[141]Cojan N L'etat de la langue dans la scarlatine au moment de l'éruption, J de méd de Paris 41: 293-294 1921

[142]Klan H Akute symmetrische Hautgangrän bei Scharlach, Klin Wchnschr 16 1639, 1937

[143]Dick G F Miller E M and Edmondson, H Gangrene in Scarlet Fever Am J Dis Child 67 374 193



Fig 15.



Fig. 16

Fig. 15.—Scarlet fever tongue on third day Coating is pierced by swollen papillae fungiformes. "Strawberry tongue. (Courtesy Dr Max Fox)

Fig. 16 —Scarlet fever fourth to fifth day Tongue is swollen, desquamated along the edges. (Courtesy Dr Max Fox.)



Fig 17



Fig

Fig 17 —Scarlet fever fifth day Tongue is clean on terior dorsum and along he edges, still coated ov he area facing he soft palat Courtesy Dr Max Fox

Fig. 18 —Scarlet fever bet een fifth and eigh h days Tongue is red, studded ith swollen papillae Raspberry ongue (Courtesy Dr M Fox)

symmetrical distribution They occur most frequently on the legs the buttocks, and the genitalia[154] occasionally on the arms, hands, face and chest.[90] They range in size from small patches to that of a whole region such as an entire foot or hand The involved skin undergoes the well known sequence of changes of gangrene pain erythema dark discoloration blistering and finally demarca



Fig 19.



Fig 20.

Fig 19 —Patches of gangrene after scarlet fever Ecthyma gangrenosum (Courtesy Dr Max Fox)
Fig 20 —Foot gangrene after scarlet fever (Courtesy D Max F)

tion and slough The hemorrhagic discoloration is not evidence of a hemorrhagic diathesis. The healing tendency is often surprising The outcome depends upon the size of the lesions the necessity for amputation and the presence of other complications The mortality is probably lower than 50 per cent[155]

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[154] H ber H J Ein Beitrag zur Genitalgangrän bei Erysipel im frühen Kindesalter Kinderärztl. Praxis 8 5-11 1937

[155] Sechter A E Multiple Gangrene of the Skin Following Scarlet Fever Arch Dermat. & Syph 27 1019 1933

The cause of this multiple symmetric gangrene is still little understood. Purpura, capillary thrombosis and thrombophlebitis[186] have in several instances been shown not to be causative. Purpura has occasionally been present.[187, 14] The findings in amputated limbs failed to demonstrate arterial block,[188, 189] and the findings of phlebitis were more suggestive of a sequel than of a cause. Possibly the explanation may be found in allergic phenomena. Gangrene has often been observed during the third or fourth week, the typical time of post-scarlatinal nephritis and has actually been seen together with it.

Another rare complication of scarlet fever is *thrombophlebitis migrans*. This is an acute febrile phlebitis usually involving the veins of both legs.[186, 190]

Circumscribed edema is another rare sequel of scarlet fever.[191] It has been known for a long time but it is apparently seen only in some epidemics. Steinbrinck[192] reported forty cases of edema of the upper lids in a recent epidemic. The swelling was in some instances so severe that it suggested subluxation of the eyeball. Involvement of the paranasal sinuses probably plays a part. All the skin changes discussed under the heading of septicemia may be observed occasionally.

Purpura, though relatively rare in scarlet fever, may occur just as in the course of other infections. It has been seen most often during the third week. The platelet count may be normal[193] or low. The mortality is high.[194] Hemorrhagic tendencies can be demonstrated early.

The *tourniquet test* is commonly positive in scarlet fever; in fact it had been devised first as a diagnostic procedure in scarlet fever.[195] Lately the capillary resistance has been investigated by E. E. Brown[196] with the more exact Dalldorf[197] suction method. It can be shown that the capillary resistance as expressed by the number of petechiae provoked under certain conditions is low at the onset and increases as the patient recovers. Age of the patient,[198] toxemia, and marked desquamation may lower the resistance.[198] Myrgård[198] saw wavelike recurrences of lowered resistance in intervals of about two weeks. He[198] demonstrated that

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[186] Henderson, E. J. and Siperstein, D. M.: Postscarlatinal Phlebitis, Am. J. Dis. Child. 20: 447, 1920.

[187] Box, Ch. R. and Massingham, R.: Purpura Haemorrhagica Complicating Scarlet Fever, Lancet 1: 795-796, 1931.

[188] Brandt, Odd: Purpura mit symmetrischer Hautnekrose bei leichter Scarlatina, Norsk Mag. f. Laegevidensk. 92: 14-16, 1931.

[189] Urbach, Erich, and Gottlieb, Philip M.: Allergy, New York, 1943, Grune & Stratton, Inc.

[190] Bates, J. V.: Postscarlatinal Thrombophlebitis Migrans, Brit. M. J. 1: 646, 1943.

[191] Zachlinsky, H.: Eine ungewöhnliche Form von Gefässschädigung beim Scharlach, München. med. Wchnschr. 84: 1960, 1936.

[192] Steinbrinck, W.: Unusual Complications (Scarlet Fever), Deutsche med. Wchnschr. 68: 1149-50, 1942.

[193] Fox, M. J. and Enzer, N.: Consideration of Phenomenon of Purpura Following Scarlet Fever, Am. J. M. Sc. 196: 831, 1938.

[194] Wood-Smith, F. G.: Purpura as Complication of Scarlet Fever, Brit. J. Child. Dis. 28: 272-281, 1931.

[195] Leede, C.: Tourniquet Test in Scarlet Fever, München. med. Wchnschr. 58: 293, 1911.

[196] Brown, E. E.: Scarlet Fever—Capillary Resistance, Arch. Pediat. 57: 443-43, 1940.

[197] Dalldorf, G.: A Criterion of Hemorrhagic Diathesis in Experimental Scurvy, J. Exper. Med. 53: 289, 1931.

[198] Myrgård, A.: Capillary Resistance and Wheal Test in Scarlet Fever, Upsala läkaref. förh. 37: 417-430, 1932; Ibid. 44: 197.

Fig. 21





Fig. 22.

Fig. 21 —Severe purpura after scarlet fever (Courtesy Dr Max F)
Fig. 22 —Severe purpura fter scarlet fever (Courtesy D Max Fox)

the absorption time of a saline wheal (McClure-Aldrich test[illegible]) is shortened especially in the beginning and in toxic cases.

Capillaroscopy shows, even in the early period the capillaries to be lengthened and engorged on the arterial side The subpapillary plexus is hyperemic and plainly visible on a brownish background The arterial flushing yields later to a status with both sections of the capillaries about equally filled with cyanotic blood. It is more than five weeks until the capillaries appear bright red again on a rosy background with sharply outlined margins and a hardly discernible subpapillary plexus.[illegible]



Fig 33 —Purpura after scarlet fever (Courtesy Dr Max Fox.)

The *Dick test* for susceptibility to scarlet fever is based on the neutralization of scarlet fever toxin in the skin of the person tested Exactly 0 1 c.c. of the test solution is injected intracutaneously[illegible] The test is considered positive if after twenty to twenty four hours an erythema however slight of not less than 10 mm in any diameter is present The reading should be done in bright light Induration is not required and may even be absent in strongly positive reactions. A positive reaction shows that the person is susceptible to scarlet fever The test is usually negative in the newborn infants of immune mothers but becomes positive during the first year of life.

[illegible] McClure W B and Aldrich C A Time Required for Disappearance of Intradermally Injected Salt Solution. J A M A [illegible] [illegible], 1923

[illegible] Müller Otfried Zur Beobachtung des Capillarkreislaufs beim Menschen, Verhandl d deutsch. Kong. f innere Med [illegible] 211 [illegible], [illegible]

The newborn infant of a nonimmune mother usually reacts positively In later life the reaction depends on the degree of exposure and silent immunization In a group of children who grow up in crowded conditions, for example in an



Fig 24 —Positive tourniquet test (Leede-Rumpel sign) in scarlet fever (Courtesy Dr Max Fox.)



Fig 25 Positive blanching test in scarlet fever (Courtesy Dr Max Fox.)

institution the incidence of susceptibility may be as low as 10 per cent and in rural groups with few contacts it may be as high as 85 per cent [20] The morbidity among children in Milwaukee with negative reactions to the Dick test was found to be only about one fourteenth of the general morbidity (Cummings after von Bormann) Convalescents of scarlet fever have negative Dick tests.

[20] von Bormann F Scharlach, Monatschr f Kinderh 83 213-261 1940.

In rare instances a mild "miniature" scarlet fever may follow the Dick test.[172]

The *blanching or Schultz-Charlton test*[173] (Auslöschphänomen) is based on the local blanching of the scarlet fever exanthem by an intracutaneous injection of normal serum, serum of convalescent scarlet fever patients or serum of diluted antitoxin in amounts of 0.1 to 0.5 c.c. "A positive reaction consists of blanching of the rash eighteen to twenty four hours after the injection in a zone surrounding the central red spot where the injection was made."[136] The positive Schultz-Charlton test [73] supports the diagnosis of scarlet fever. The area of skin which has been blanched does not peel.[74]

There is still controversy about the limitations of these two tests.[175, 76]

Pathology.—There is edema, hyperemia and inflammatory infiltration especially around the follicles and sweat glands. Endothelium-covered fibrous exudates have been seen in the walls of small veins in scarlet fever as well as in other pyogenic infections,[177] especially subacute bacterial endocarditis. Parakeratosis precedes the peeling.[61]

It is remarkable that hemolytic streptococci are common in the superficial scales of the peeling skin but could rarely be found in the deeper layers.[7] This may mean that the scales become infected from without, and that the living skin during the desquamation is no longer infected. Recently streptococci have been demonstrated in the endothelial cells of blood and lymphatic capillaries and in adjacent cells.[79] The desquamated skin is not considered contagious.[144]

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[172] Wallis, H. R. E. Miniature Scarlet Fever After Dick Test, Lancet 2 219 1948.

[173] Schultz, W. and Charlton, W. Serologische Beobachtungen am Scharlachexanthem, Ztschr f. Kinderh. 17 328-333 1918.

[174] Fanconi, G. Beiträge zum Scharlachproblem, Abhandlungen aus der Kinderheilkunde und ihren Grenzgebieten, H 12 Berlin, 1926, S. Karger.

[175] Reisman, H. A. and Berkow, A. Dick Test, Arch. Pediat. 58 190-93, 1941.

[176] Press, E., and Litvak, A. M. Schultz-Charlton and Dick Test in Scarlet Fever, Arch. Pediat. 58: 194-197, 1941.

[177] Siegmund, H. Gefässwandreaktionen, Verhandl d. deutsch. path. Gesellsch. 20 261 1925.

[178] Kanevskaya, M. J. Presence of Streptococci in Scales of Scarlet Fever Patients, J.A.M.A. 89 1011, 1927.

[179] Tornack, J. H. Etiology and Pathogenesis of Scarlet Fever. Histologically Demonstrated Storage of Coccus-like Structures in Endothelial Cells of Skin, Mucous Membrane and Lymph Nodes, Klin. Wchnschr. 21 481 1942.

Chapter III

SYSTEMIC INFECTIONS

Lobar Pneumonia

In none of the various types of lobar pneumonia are skin manifestations important with the exception of *herpes simplex* (herpes febrilis herpes symptomaticus) which occurs in a high percentage, between the second and fifth day usually on the lips. The eruption appears as groups of clear vesicles on a red slightly edematous base. After one to two days the vesicles become pustular often confluent and finally they dry up The crusts come off after about five days usually without leaving a scar The incidence of herpes varies according to the type of pneumococcus. Among 500 cases of lobar pneumonia of all types 30 per cent were herpetic [160] This incidence was observed in London England The herpes incidence among 500 cases in New York was only 12 per cent,[161] while many older mostly German figures run as high as 40 or even 50 per cent. J A Montgomery [160] analyzed the occurrence of herpes in 500 cases of lobar pneumonia with regard to *types of pneumococci* While the incidence of herpes is about the same (30 per cent) in all types the mortality in the herpetic is lower than in the nonherpetic cases, especially in type I In which the mortality is less than one-sixth of that of the nonherpetic of the same group The relatively favorable prognosis of herpetic pneumonia has been well established [162] [163] [164] for a long time Montgomery [160] records a mortality of 14 per cent in the herpetic group and 16 per cent in the total Schwartz's [161] corresponding figures are 5 and 25 per cent which is closer to the old figures. [162]

Herpes is uncommon in acute Friedländer pneumonia which has a high mortality (75 per cent) [165]

Petechiae occur in severe cases of pneumococcic sepsis. E. Fraenkel [166] examined such lesions in two fatal cases. Clinically they seemed to be only petechiae the histological structure suggested bacillary metastases but no pneumococci could be found E Fraenkel [166] emphasizes the rarity of skin manifestations in pneumococcic infections He believes that the skin enjoys a certain immunity to pneumococci since skin metastases are lacking even when specific metastases are found in many other organs.

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[160] Montgomery J A Herpes Febrilis in Lobar Pneumonia Lancet 1 1041 1042, 1939

[161] Schwartz J Pneumonia 500 Cases M Rec 147 19-200 1938

[162] Schönfeld W Die klinische Bedeutung des Herpes simplex für andere Krankheiten und physiologische Zustände Therap-Chl med Monatschr 12 296-303 1937

[163] Naegeli O Herpes Simplex, München med Wchnschr 83 339-344 1936.

[164] Goodall F Life-Story of Simple Herpes, Lancet 1 906 1939.

[165] Solomon S Chronic Friedländer Infection of the Lungs, J A.M A 115 1527 1536, 1940.

[166] Fraenkel E Metastatische Dermatosen bei akuter bakterieller Allgemeinerkrankung. Ztschr f. Hyg u. Infectionskrankh 76 159 1914

Equally rare are diffuse or maculovesicular *erythemas*[187, 188] A few times, pneumococci have been found in the skin lesions. The rare varicella resembling rashes may be generalized herpes.[189]

As long as the fever is high the skin remains hot and dry It is an old observation that the *cheek on the side of the involved lung is redder* than the other The most plausible explanation is that the patient often lies on the involved side in order to keep this painful side quiet but this explanation is not always correct.[187] Only during and after the crisis do profuse sweats occur especially in juveniles. These sweats are sometimes followed by miliaria rubra.

Systemic Pyocyaneus Infection

In spite of the common infection of wounds with *Pseudomonas aeruginosa* (*Bacillus pyocyaneus*) and of the frequent saprophytism of this microorganism systemic infection is rare and occurs usually in debilitated persons [illegible, 191, 192] Almost all organs may become infected the skin often being involved The skin manifestations of severe pyocyaneus sepsis do not differ from those of other pyemids. However there is a characteristic dermatosis *ecthyma gangraenosum* which is known to occur in the wake of measles and various other infections and cachectic states (see Fig 19) especially in children and which in a considerable number of instances has been shown to be caused by *Pseudomonas aeruginosa* Its character as a skin manifestation of a generalized infection is shown by many analogous autopsy findings in interdal organs.[illegible] The skin lesions start as papules, but soon become bullous and hemorrhagic and form round sharply outlined necrotic and painful ulcers which may reach the subcutaneous tissues and even invade the muscles. Petechiae and large ecchymoses are supposed to be characteristic.[illegible] Their number varies from one lesion to exanthematic dissemination Healing has seldom been observed since most of these patients die within a short time The general course is that of a septic toxemia.[illegible]

The histologic examination shows many gram-negative bacilli in the outer layer of the blood vessels especially of the arteries.[illegible] Atypical apparently hematogenous skin infections with pyocyaneus have occasionally been described[193, illegible]

Meningococcic Meningitis (Cerebrospinal Fever)

After an incubation period of a few days the onset is usually sudden with high fever severe headache, and vomiting Meningitic symptoms ap-

[187] Howard C P and Mills E S Pneumonia, Oxford Monographs, Vol X New York 1920, Oxford University Press

[188] Schmidt-LaBaume F and Ott C Zur Klinik, Histologie und Pathogenese der Pneumok Exanthematheme Arch f Dermat Syph 169 431-438, 1933

[189] Sharpe Wm S Eruption Resembling Varicella in Lobar Pneumonia, Brit M J 1 14, 1922.

[190] Bruck, C Die Pyocyaneuserkrankungen der Haut Handb. d H Gk 9 1 126-144, 1929.

[191] Kline B S and Speckh A S Three Fatal Cases of Bacillus Pyocyaneus Infection J A.M.A. 90 823-832, 1928

[192] Lewandowsky F Ueber die Hautaffektion bei Erwachsenen, verursacht durch d Bacillus pyocyaneus, München med Wchnschr 1907 II 2273

[193] Frei, W and Wiener K Ein Fall von eigenartiger Hauterkrankung aus der Gruppe des Ecthyma gangraenosum (mit Pyocyaneusbefund Arch f Dermat Syph. 134 106-118 1921.

pear after from two to four days. There is irregularity of the pulse and respiration painful stiffness of the muscles abolition of superficial abdominal reflexes, insomnia and restlessness. The patient lies on his side with the knees drawn up The leukocytosis may be very high

After the first week the patient's restlessness often changes to stupor The recovery is gradual the course is varying death may occur in any stage

Before the advent of the sulfonamides the mortality rate was as high as 49 per cent in children under the age of one year and from 10 to 20 per cent above this age.[194] Today the mortality rate has been lowered to 2 per cent[195] and even less.[196]

The sulfonamides and penicillin are the drugs of choice in the treatment of meningococcic infections.

Dermadromes.—A variety of rashes occur with varying incidence Figures between 91 [97] and 100 per cent[198] are available [199]



Fig 26.—Meningococci meningitis. Purpuric rash (Courtesy Dr Ma Fox.)

Of importance is a *purpuric rash* consisting sometimes of only a few petechiae occasionally of very many hemorrhagic spots resembling flea bites or larger The *rash often being scanty one should look for purpuric lesions on the chest armpits,* abdomen thighs buttocks and hips A single petechia of the conjunctiva may

[194]Worster Drought C and Kennedy A M Cerebro-spinal Fever London, 1919 A. & C. Black Ltd

[195]Thomas H M J Meningococcic Meningitis and Septicemia, J A M A 123 264 272, 1943.

[196]Hill, L W and Lever H S Meningococcic Infection in an Army Camp J A.M A. 123 9 14, 1943

[97]Blackerby P F and Caudill F W Epidemiologic Study of Approximately 400 Cases of Cerebrospinal Meningitis Comparati Valu of A titoxin and Antibacterial Serum South. M J 31 161 169 1939

[198]Dickson, R C M kinnon N E Magner D and McGillivray N D Meningococcal Infection Lancet 1941 II 631-634

be the only lesion.[194] The purpuric rash may develop exceedingly rapidly almost under the eyes of the observer There is no parallel between the extent of the rash and the severity of the infection [194] as had been thought by many older authors.[194] However purpura seems to be of more ominous significance than petechiae [194] and the fulminating purpura of the Waterhouse Friderichsen syndrome is an almost certain omen of a fatal outcome. Larger purpuric lesions may become vesicular bullous or ulcerative. Petechiae are not restricted to the skin. They may appear in the conjunctivae in the oral mucosa and in the serous membranes. The great significance of the purpuric rash lies in the fact that the



Fig. 27 —Meningococcic meningitis. Papulohemorrhagic rash. Courtesy Dr Max Fox)

lesions are true *metastatic bacillary lesions* not hemorrhages due to lowered capillary resistance of toxic cause. E. Fraenkel[67] found meningococci in the cel lular infiltrate of the petechial efflorescences He also demonstrated Friedlander bacilli in the purpuric skin lesions of a case of meningitis caused by this microorganism Since then the search for microorganisms in purpuric lesions has become a diagnostic method Tompkins[195] and McLean and Caffey[196] were able to demonstrate diplococci in smears in 80 per cent of their cases. *To obtain material for the smear* a purpuric spot is gently blanched between two fingers and pricked with a fine hypodermic needle Then some serum is squeezed out and

[194] Newcomer W and Frame E M Summary of 80 Cases of Cerebrospinal Fever U S N M Bull. 41 966-972 1943

[195] Tompkins V N Diagnostic Value of Smears From Purpuric Lesions of Skin in Meningococcic Disease J A M A 123 31-33 1943

[196] McLean, S and *Caffey J* Endemic Purpuric Meningococcus Bacteremia in Early Life The Diagnostic Value of Smears From Purpuric Lesions, Am J Dis Child 42i 1053-1074 1931

Fig. 28.

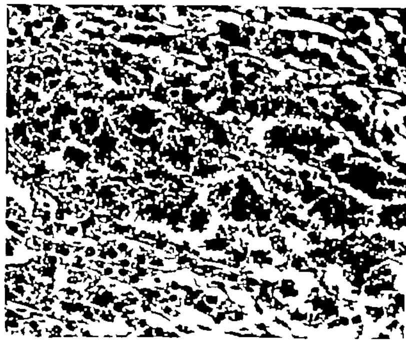




Fig 29

Fig 28 —Fulminating meningococcemia (Waterhouse-Friderichsen syndrome) Engorgement of capillaries in zona fasciculata with early hemorrhagic extravasation (From Pratt Thomas, Kelley and Gaines South M J 1945)

Fig 29 —Fulminating meningococcemia (Waterhouse-Friderichsen syndrome) Meningococci in polymorphonuclear leukocyte in smear from purpuric lesion (Gram stain, X2000) (From Pratt Thomas, Kelley and Gaines South M J 1945)

placed on a slide. Quantity is not an object but it is important that the prick be superficial and the exudate not diluted by peripheral blood. The smear is stained with Giemsa or Wright stain. The smears taken from lesions other than purpuric ones are usually negative.

The second type of cutaneous manifestation in meningococcic infection is a *maculopapular rash* which is sometimes seen as early as on the first day of illness. It is described as consisting of discrete slightly palpable rather



Fig. 30.—Herpes labialis in meningococcus meningitis. (Courtesy Dr Max Fox.)

scanty (rarely more than a dozen) inconspicuous, round well-defined pink spots of from 5 to 35 mm in diameter.[illegible] The eruption may coincide with or closely follow the onset or a recurrence of the fever and the general symptoms of the infection.[illegible] The lesions are most often found on the trunk and along the extremities especially about the shoulders. They are tender, do not appear in crops and vanish within about four days. Sometimes they become purpuric in the center and palpable like erythema nodosum. Only rarely have they a morbilliform character but they often resemble the rose spots of typhoid fever to such a degree that all other diagnostic factors must be considered in order to avoid errors. An early appearance especially on the extremities seems to indicate meningitis rather than typhoid. During epidemics this rash alone is considered characteristic enough to establish the diagnosis of meningococcic septicemia.

[illegible] Herrick, W. W. Meningococcus Infections. Oxford Medicine. Vol. I. New York, 1940. Oxford University Press, pp. 71-104.

[illegible] Priest, R. 204 Cases of Cerebrospinal Fever. J. Roy. Army M. Corps 76: 249-260, 1941.

Several *other types of cutaneous lesions* have been described. They include transient rubelliform[194] or scarlatiniform erythematous rashes hemorrhagic vesicles hemorrhagic gangrene [195] and a peculiar urticaria consisting of a large wheal on the buttocks The latter which has been seen by several authors was supposed to be a foreshadowing of a fatal outcome [194] in the pre-sulfa era *Herpes* often extensive and in atypical distribution is present in about one-third of the cases. While often seen on the fourth day it may appear at any time after thirty-six hours from the onset.[194] *Herpes zoster* involving almost all of the known sites is conspicuously frequent as in lobar pneumonia. The vesicles may contain meningococci. The belief that herpes is a favorable sign was held by many of the earlier authors however this is not true. The opinion was probably caused by the relatively favorable prognosis of herpetic pneumonia

Gonorrhea

Gonorrhea is predominantly a disease of the mucous membranes Cutaneous involvements are rare. Ulcerations of the genital skin folliculitis and abscesses or pseudoabscesses are mostly due to exogenous infection of epithelial ducts or follicles from the gonorrheic urethra. Hematogenous gonococcic infections of the skin can be grouped under *transitory* urticarial erythematous or hemorrhagic exanthems of the type seen in other bacteremias and *keratotic* eruptions which are characteristic of gonorrhea and hardly known in other diseases.

There is a great morphologic variety of exanthems in the former group which makes it difficult to correlate the rash with the gonorrhea by any other evidence than coexistence even after the possibility of an eruption from sandalwood oil cubebs and similar drugs used in gonorrhea has been ruled out. The eruptions which have been described have been seen not only in febrile septic cases but also in relatively mild infections If they repeatedly come and go with exacerbations of the gonorrheic infection the connection is quite obvious. The best proof of the specific nature of the questioned eruption is of course the finding of gonococci in the skin lesions. This has been accomplished in several cases [196] In one case of septicemia caused by gonococci a macular rash was seen together with arthritis and endocarditis. [87] Gonococci could be demonstrated in the blood in the endocardium and in the erythematous spots. Kerl[198] saw simple erythema together with epididymitis. Scarlatiniform [199] urticarial eruptions with hemorrhagic tendencies occupying the lower legs [21] vesicular [199] vesiculohemorrhagic,[201]

[194] Silverthorne N and Cameron, C Meningococcus I fection, J Pediat 18 618-627 1941

[195] Potiron, B Claude, P A banel, J and de Balmann, A Meningococcemic Gangrenous Purpura Associated With Cerebrospinal Meningitis Cure by Serotherapy Sulfathiazide and Vitamin A, Bull et mém Soc méd d. hôp de Paris 55 891 896 1939

[196] Margolin, E S Gonorrheal Dermatitis as Part of Systemic Gonorrhea, Urol & Cutan Rev 47 812-814 1943

[197] Dorner L Gonokokkensepsis, München med Wchnschr 70: 1060, 1923.

[198] K rl, W Gonokokkenexanthem, Zbl 49: 557 1935

[199] Cojan, G Septicémie gonococcique récidivante vec déterminations rares, Rev roum. d' Urol 2 495-502 1936 Zbl 56 346

[200] Sullivan, S J Cutaneous Eruptions Accompanying Gonorrhea Case f Hemorrhagic Exanthem., Urol & Cutan Rev 38 93-95 1934

[201] Keil, H. Type f Gonococcal Bacteremia With Characteristic Hemorrhagic Vesiculo-Pustular and Bullous Skin Lesions, Quart J Med. 7 1 16 1938

hemorrhagic,[212,213,222] nodular[214] herpetiform[215] erythema exudativum multiforme and erythema nodosum resembling rashes[216,213,217] are an illustration of the multiplicity of appearances which these bacteremic eruptions may assume.[222] Sometimes these rashes show very distinctly that they are caused by focal infections. Sullivan[218] observed an acute eruption of suppurating nodules after dilatation of a urethral stricture



Fig. 21.—Keratosis gonorrhoica (From Epstein, E. Am J Syph. 21 142, 1937.)

In some instances gonococci have been found in purpuric lesions (Brunsgard and Tjotta after Langer[215]) and in abscesses. Icterus is mentioned in several cases.[21] In spite of the great morphologic variety these bacteremic gonococcids are rare and do not differ much from the eruptions seen in pyogenic septicemia.

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[212] Wiedmann, A Beiträge zur Pathologie der Gefässerkrankungen der Haut die gewebliche Veränderungen beim hämorrhagischen Gonokokkenexanthem mit besonderer Berücksichtigung der Gefässveränderungen Dermat Wchnschr 98: 441-447 1934

[213] Ladany E and Hughes, J D Etiologic Considerations of Keratosis Blennorrhagica, Report of Case in Which Penicillin was Used. Arch Dermat & Syph 54 160-170, 1946

Decastello A and Wehmann, O Febris maculosa intermittens (Meningo-und Gonokokkämie Fièvre intermittente pseudopalud'enne Meningokokken-Lenta-Sepsis, Wien. Arch f. inn. Med 20: 429-472 1930

[215] Langer E Hautkrankheiten bei Gonorrhoe Handb d H u Gk. 20, 2: 40-74, 1930

[216] Edel. Aetiologie des Erythema nodosum Zbl 38 712, 1931.

[217] Ichikawa T and Ohmori. Beiträge zur Kenntnis des Gonokokkenexanthems, Jap. J Dermat. & Urol 34: 511-5 7 1933 Zbl 48 281

[218] Murdock, J G A Case of Keratoderma Blennorrhagicum, Brit. J Ven. Dis. 12: 243-245 1936

Of much greater dermatological interest are the rare *hyperkeratoses* in gonorrhea keratoderma blennorrhagicum (keratosis blennorrhagica) Only 166 cases have been described since Vidal's[217] first observations in 1893 It has been estimated that keratosis blennorrhagica occurs about once in 5,500 cases of gonorrhea.[218] These dermatoses form a clinical picture which is almost exclusively connected with gonorrhea and it certainly is one of the most characteristic dermadromes peculiar to any one infection Most of the patients are young men suffering from chronic urethral gonorrhea, usually with complications particularly arthritis and ocular complications. The gonorrheal infection frequently is of long standing [219] even many years when the rash breaks out. The eruption often starts with a papulovesicular exanthem In some cases the primary lesion is described as a small glossy pink papule resembling a droplet of wax. The vesicles dry up but instead of peeling as one would expect they transform into pseudopustular lesions which look yellow but do not contain pus. These become keratoses and finally form a large hobnail-shaped conical lesion of layer texture. The keratoses are rupioid limpet-shaped and have a flat or umbilicated top with a yellow center which contains brittle white horny detritus. The bottom layer of horny material forms a yellow clifflike ring around the lesion which is sometimes surrounded by an inflammatory areola The keratotic top is easy to remove leaving a shallow pink slightly moist or gelatinous[221] erosion Keratoses at these areas are often of follicular origin The lesions may grow slowly from pinhead size to several centimeters in diameter and they may coalesce into large rough hyperkeratotic plaques mostly on the soles and around the big joints particularly if the joints are inflamed In these plaques many pseudopustular cavities may be found The extremities are in some cases studded with button or medallion-shaped lesions which may reach 1 cm in thickness The *penis* is a site of predilection for the gonorrheic dermadromes [illegible] which may appear as typical keratotic papules *On the glans and on the inner surface of the foreskin* they may appear as glossy red flat papules or macules [illegible] which may coalesce into polycyclic patches. Sometimes the keratotic character of these lesions is marked by a grayish macerated crumbling horny top layer (balanitis circinata) The keratoderma may even be restricted to such penile eruptions. These lesions occasionally resemble a syphilitic chancre (Tullien after Langer[illegible]) or lichen planus.

The *scalp* sometimes becomes involved [224] The *nails*[225-226] often become thick dull and brittle and subungual keratoses may raise or loosen the nail The

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[217] Vidal, E Éruption généralisée de croûtes cornées avec chute des ongles Ann d dermat et syph 4 3 1893

[218] Stroominger L Quelques considérations sur la kératose blennorragique J d urol 32 251 257 1931

[219] Scholtz M Gonorrheal Keratoderma, Arch Derm & Syph 21 961-969 1930

[220] Arning and Meyer Delius Gon Hyperkeratose Balanitis circinata gonorrhoica b retrahierter Vorhaut Arch f Dermat Syph 108 3-26 1911

[221] Sherman, W L Blumenthal F and Heidenreich, J Blennorrhagic Balanitiform Keratoderma, Arch Dermat & Syph 39 422-429 1939

[222] Frühwald Keratodermia blennorrhagica, Zbl 51 262 1935

[223] Cederberg, A Abortivformen der gonorrhoischen Keratodermien Act dermat venereol 13 43-52, 1932

[224] Cornbleet T and Pace E R Keratoderma Blennorrhagicum Arch Derma & Syph 29 291 1934

whole nail bed even the entire tips of the fingers or toes may be covered with the keratotic masses. In several instances sharply contoured round or poly cyclic irregular grayish patches with erythematous borders have been observed on the palate and on the buccal *mucosa*.[illegible]

The general *distribution* of the rash is largely symmetrical. All *degrees* of involvement from a single keratotic patch on the penis[illegible] to universal erythroderma have been seen Naturally the discomfort and suffering of the patient depends on the extent and the degree of tenderness of the individual lesions. The appearance of new crops is usually coupled with renewed arthritic attacks. The eruption may last months or years depending mainly on the course of the gonorrhea but also on the degree of involvement of the skin. The majority of the cases of keratosis blennorrhagica finally heal but about 10 per cent fatalities have been recorded [illegible]

The *histological* picture is characterized by heavy keratosis and parakeratosis with formation of cavities. There are edema and cellular infiltration in the papillary stratum.

Gonococci have been found in typical lesions in at least seventeen instances [illegible] although much more often the efforts to find the microorganisms have been in vain The positive findings are definite proof of the hematogenous infectious nature of the eruptions which already had been suggested by the clinical relationship to arthritis endogenous conjunctivitis and iritis and the symmetric and follicular distribution on the extremities. Occasional observations give further support to the conception of a focal infection Scholtz[illegible] saw a flare-up of the joint symptoms, and the appearance of a new crop of heavily crusted lesions after 8 c.c. of gonorrheal vaccine (instead of 0 8 c.c.) had been administered by mistake. Similar reactions have been seen after treatment with vaccine [illegible] and warnings against vaccine therapy of such hyperergic patients have been voiced [illegible] The extirpation of the infected seminal vesicles resulted in the healing of a gonorrheic exanthem and the dilatation of a urethral infiltration or other urethral manipulations produced flare-ups[illegible] in at least five instances[illegible] (Lewin after Langer[illegible]) These observations are not only evidence that the *gonorrheic* keratodermas are caused by focal infection but they show the role allergy plays in producing the characteristic clinical entity The scarcity of the gonococcus has its analogy in the paucity of microbes in tuberculids trichophytids and other

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[illegible] Frei, W Gon. Exanthem der Mundschleimhaut, Balanitis circinata gonorrhoica bei Ohrenschleimhaut[illegible] Zbl 44 271 1933

[illegible] Oole and Driver Keratoderma Blennorrhagica Arch Derm & Syph 19: 636-637 1929.

[illegible] Barrett C O Keratoderma Blennorrhagicum with cases Gonococcus in Local Lesions, Arch Derma & Syph 22: 637-638, 1930.

[illegible] Combes, F C and Behrman, H T Use of Vitamin A in Keratosis Blennorrhagica Arch Dermat & Syph 46: 723-33, 1942

[illegible] Scarpazzoni, T Cheratodermia blenorragica Gior ital di dermat sif 1 36-39, 1931 Zbl 39 302

[illegible] Malherbe H Urétrite à gonocoque récidivantes arthropathies multiples troubles trophiques J d mal cutan et syph 1900 Gaz méd Nantes 1900

ida. The complement fixation reaction has several times been found to be positive.[303-306]

The provocation of specific lesions by irritation with phenol[307] (not confirmed by Keim[308]), by herpes lesions (Buschke after Langer,[314] Gjessing after Langer[315])



Fig. 23.—Keratosis blennorrhagica without gonorrhea. (From Lever, W. F. and Crawford, G. Marshall. Arch. Dermat. 1944.)

by inoculation with gonococcic pus and by maceration with wet dressings[309] demonstrates the changed capacity to react which has developed under the influence of the infection. Possibly the balanitic keratoses are caused by inoculation of gonococcic pus into an allergic skin which has acquired the peculiar keratogenic tendency.

Gay and Jacob. Keratoderma Blennorrhagicum. Arch. Dermat. & Syph. 21: 703-704, 1930.
Löhe, H. and Rosenfeld, H. Klinische und pathologisch-chemische Untersuchungen über die Hyperkeratosenbildung bei Gonorrhoe und bei Psoriasis pustulosa arthropathica. Derm. Ztschr. 55: 353-374, 1929.
Beeson, B. B. and Ebert, M. H. Keratoderma Blennorrhagicum. Arch. Dermat. & Syph. 21: 739-741, 193[illegible].
Levy, D. and Percival, G. H. Keratoderma Blennorrhagicum. Lancet 1932 II: 1116-1121.
Kutcalij, O. Sekundärbefund der Keratosis Gonorrhoica. Jap. J. Derm. & Urol. 33: 94, 1933. Zbl. 43: 792.
Klein, H. L. Histogenesis of Keratoderma Blennorrhagicum. Arch. Dermat. & Syph. 9: 423, 1924.
Lojander, W. Ueber Keratodermien im Anschluss an Gelenkaffektionen gonorrhoischen und nichtgonorrhoischen Ursprungs. Act. derm.-venereol. 8: 327-334, 1927.

The predominance of the male sex in a ratio of 15 3 1[337] and some autopsy findings seem to support the assumption of endocrine influences.[336,337]

In a small number of clinically typical cases it has not been possible to secure the diagnosis of a gonorrheic infection[[illegible]] nor to obtain a suggestive history In the cases with a history of gonorrhea even many years prior to the dermatosis the existence of gonorrhea can hardly be ruled out



Fig. 33 —Reiter disease Lesions are first flaccid pustules containing macerated epithelial cells, later hyperkeratotic (From Lever W F and Crawford G Marshall Arch Derma 1944)

Lately several cases of the syndrome arthritis urethritis, conjunctivitis and keratoderma have been described in which all efforts to corroborate gonorrheic infection failed.[[illegible]] These cases belong at least in part to *Reiter's disease* the etiology of which unknown Penicillin is ineffective

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[[illegible]] Bone and [illegible] [illegible] Keratosis [illegible] [illegible] [illegible]
Lever W F and Crawford [illegible] Keratoma Blennorrhagica Without Gonorrhea Reiter Disease Arch Dermat & Syph 49 [illegible] 19[illegible]
[[illegible]] Ferguson A G and [illegible] Frank J Keratoderma Blennorrhagica Some Further Observations as to Etiology Brit J Dermat [illegible] 28 [illegible]
[[illegible]] [illegible] J C Reiter [illegible] J Urol [illegible] 1945

The similarity of gonorrheic keratosis to arthropathic psoriasis may be considerable. However the history and presence of psoriasis, the vesicular primary lesions, the degree of keratosis, the distribution, the gonorrheic evidence, and a biopsy will secure the diagnosis. In psoriasis the arthritis follows the skin lesions while gonorrheal arthritis is more likely to precede the exanthema.[194] Rupioid or tertiary syphilis may have to be ruled out.



Fig. 24 —Reiter's disease. Keratotic round lesions on glans penis. (Courtesy Dr. Sargen.)

The treatment is to heal the gonorrheic infection. The treatment with vaccines should be undertaken with the greatest caution to prevent exacerbations. Many authors stress the importance of proper nutrition and nursing of these patients who are often extremely weak, uncomfortable, emaciated, and anemic. Vitamin A had good effect in one case after sulfathiazole had failed.[195] As local measures salicylic acid in plasters and ointments to remove the excessive keratotic masses should be applied. Great care should be taken to avoid irritation and maceration of normal skin in order to prevent provocation of new keratoses. Penicillin has in the only reported case of its application in keratosis blennorrhagica[195] failed to influence the course. It must be given further trial with high doses and prolonged treatment.

Poliomyelitis

Rashes are not a characteristic of infantile paralysis. Red dermographism (tache cérébrale) is mentioned.[196]

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194 Epstein, E.: Differential Diagnosis of Keratosis Blennorrhagica and Psoriasis Arthropathica, Arch. Dermat. & Syph. 40: 547-550, 1939.

195 Zelatsky, E. M.: Keratodermia Blennorrhagicum, Am. J. Syph. Gonor. & Ven. Dis. 29: 281, 1945.

196 Wilson, J. L.: Poliomyelitis, Oxford Medicine, vol. V, New York, 1940, Oxford University Press, pp. 107-124.

Erysipelas

Singer[346] observed various simple polymorphous or purpuric erythemas in the course of 25 per cent of his erysipelas cases No substantial confirmation of this observation has become known

Chancroid

Lennhoff[347] reported a case of erythema nodosum-like eruption in a case of ulcus molle. The secondary lesions ulcerated contained Ducrey Unna bacilli and were inoculable into the normal skin of the patient. Werther[348] succeeded in demonstrating the streptobacillus in the blood in a case of disseminated ulcera mollia Hematogenous infection from a soft chancre seems to be exceedingly rare since hardly any other well-corroborated cases have become known.

Typhoid Fever

Typhoid fever is an endemic and epidemic, contagious, food or water borne disease caused by a gram negative motile bacillus *Eberthella typhi* After an incubation period of from one to two weeks the disease starts insidiously with a slowly rising fever which reaches a high level with small morning remissions during the second week and diminishes by lysis during the third week or later The pulse is much slower than the temperature would lead one to expect.

Abdominal and splenic tenderness and diarrhea with pea-soup-like stools are the most common symptoms. Delirium and severe general emaciation are other clinical features at the height of the disease.

Complications in almost every organ are known and the severity of the disease varies from symptomless carriers and walking typhoid to fatal cases. The outstanding post mortem finding is hyperplasia of Peyer s patches in the small and large bowel. The hyperplasia often results in ulceration which may lead to hemorrhage perforation and peritonitis. The spleen is enlarged and there is fatty degeneration of the liver

Dermadromes.—Typhoid fever has a characteristic exanthem known as *rose spots* or roseola. The rash consists of thin almost macular papules which blanch on pressure and measure hardly more than one-half centimeter in diam eter They appear in small crops and last about three to five days. While the crops come and go about one to two dozen lesions are usually present from the end of the first week of the disease to the second or third week, rarely outlasting the fever They almost always disappear without desquamation or pigmenta tion In rare instances the rose spots are papular[349,350] hemorrhagic, or vesicular

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[347] Lennhoff, R. Ueber einen Fall von knotigen vereiternden hämatogenen Metastasen an den Unterschenkeln bei weichem Schanker Arch f Dermat Syph 131 80-84 1921

[348] Werther Multiple disseminiert Ulcera mollia, bei welchen Streptobacillen aus dem Blute gezüchtet wurden, Zbl 37 732 1931

[349] Dore E Cutaneous Affections in Various Diseases, Brit J Dermat, 18 420, 1906

[350] Rosenthal, S K Zur Kenntnis seltener Hauteruptionen bei typhösen Erkrankungen, Dermat. Wchnschr 89 961-963 1929

The eruption is mostly concentrated on the abdomen the chest and the back, and it usually appears first on these areas. Only in exceptionally dense eruptions does it invade the limbs and then the density decreases distally The neck is rarely involved and the face remains free.[381] The exanthem is a scanty one compared with those of other infections particularly in small children The number of rose spots seems to vary in epidemics. An abundant rash is no indication of the severity of the infection [382,383] While some good observers failed to detect the exanthem in as high as 20 per cent,[382] other authors (Eichorst after Miller[383]) were able to detect rose spots in all the 2 000 cases of a series.

The *pathological* examination of the lesion shows a superficial rather than mainly leukocytic perivascular infiltrate in the upper corium which in the rare papular lesions invades the epidermis.[87,384,385,386] The lack of plasma cells is striking [384] Typhoid bacilli are in rare instances seen as *metastatic deposits in* the lymphatic spaces or between the cutis and the epidermis [384] which may become separated within the small area of the rose spots. Frequently they can be cul tured from the rose spots However with the development of the blood culture this method has lost its diagnostic importance.[385]

Hemorrhagic exanthems in typhoid are rare H Curschmann[382] saw only 6 among 2 000 cases (all six patients died) The percentage was higher in other epidemics (McCrae after Miller[383]) Curschmann's[382] observation of a small epidemic of typhoid with purpura is remarkable A mother and six children all showed purpuric rashes. While their cases took a favorable course the father developed a hemorrhagic bullous eruption and died [386] Röper[387] saw a similar case *with extreme thrombopenia and leukopenia. The bullae appeared especially* over the bony prominences

Scarlatiniform morbilliform papular[388] varioliform [389] and other rashes may occur[38] (Da Costa after Dore[349]) but they are rare. The *absence of herpes* is notable. Osler[38] saw herpes only 20 times in 1,500 cases Several clinicians feel that the presence of herpes should be a warning against a premature diagnosis of typhoid fever

Miliaria crystallina (sudamina) is supposed to be more common than in other infections. The content of the clear vesicles is neutral or slightly acid The blisters dry up and are destroyed before they become pustular Miliaria appears mainly on the abdomen the chest and the thighs, not on the face [381] Urticaria is an occasional (0 3 per cent) complication *Furunculosis* and *decubitus*

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[382] Curschmann, H Der Unterleibstyphus in Nothnagel Speciell. Pathologie und Therapie, vol III Vienna, 1902, Alfred Hölder pp 108-110

[383] Miller J L Typhoid Fever Oxford Medicine vol IV New York 1940 Oxford University Press pp 666-730

[384] Poehlmann, A Über Typhus- und Paratyphusroseolen Arch f Dermat u. Syph 131 431-452 1921

[385] Fraenkel E Roseola typhosa und paratyphosa, München med Wchnschr 9 325-329, 1916

[386] Baerthlein, K Abdominal Typhus, Kolle und Wassermann Handbuch der pathogenen Mikroorganismen vol III 2 p 1214, 1931

[387] Röper K Bullöse hämorrhagische Dermatose bei Typhus, München med Wchnschr 31 2036-2037 1931

[388] Trauwitsch B Typhus abdominalis mit atypischem Exanthem, München med Wchnschr 73 2249-2250, 1926

[389] Gottschalk O Varioloartiges Initialexanthem bei Typhus abdominalis, München. med. Wchnschr 73: 17 1926

are common and troublesome. Curschmann[illegible] described a type of bedsore which he often saw as a subcutaneous decubitus. Subcutaneous abscesses developed in the pressure areas and later opened forming multiple sinuses. Both furunculosis and decubitus can to a certain extent, be prevented by meticulous nursing care Mottled sievelike pigmentation and depigmentation has often been seen on the abdomen of children after typhoid fever [illegible]

Noma and other buccal ulcerations are very rare complications. Other *ulcerations* include ulcus vulvae acutum[illegible] and a similar vulvar ulceration[illegible] with raised edges and a necrotic floor

The *tongue* is furred especially at the height of the disease. The edges and the tip are often clean in contrast to the dorsum.

The face is flushed in the early period and dull and listless later [illegible] Osler and Christian[illegible] emphasize the yellow color of the palms and soles and mention a very distinctive musty odor of the skin The author has been unable to find more exact observations on this odor and in attending many patients with typhoid he has been unable to notice it.

Effluvium capillorum is very common after typhoid but only rarely does it reach extreme degrees with complete loss of the hair *Beau's lines* of the nails are usually noticeable but shedding of the nails is rare.

The diagnosis of typhoid fever cannot rest upon the roseola alone but it constitutes a most valuable diagnostic criterion For most practical purposes the paucity of the lesions the complete blanching on pressure the distribution on the trunk and especially the abdomen and the appearance of recurring crops will suffice to distinguish the roseola in typhoid from the rash in spotted typhus and other rickettsial diseases. In the rickettsioses the more abundant rash appears within two days in one outbreak is usually hemorrhagic, and the individual lesion is less neat and regular There is more tendency to involve the extremities especially the more distal parts [illegible]

A negative Wassermann and lack of other syphilitic manifestations will rule out syphilitic roseola which is usually abundant and has larger individual lesions.

Paratyphoid Fever

The clinical picture in paratyphoid fever including the rash resembles typhoid fever The rash was seen in about one-half of the cases of an epidemic recently observed in England.[illegible]

The *rose spots* in paratyphoid are more numerous than in typhoid They occasionally cover even the hands and cheeks and desquamation occurs. Like the rose spots in typhoid fever the roseolae of paratyphoid are true bacterial

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[illegible] Henó, Van J Hauterscheinungen bei dem infantilen Abdominaltyphus, Orvosképzés 24, Halalos, Special Issue 33-24 1934 Zbl 51 22

[illegible] Berlin, O Ulcus vulvae acutum in Typhoid Fever Arch. Dermat. & Syph. 29: 89-91 1939

[illegible] Zannelli, P Ulcerazioni specifiche dei genitali esterni di una malata di febbre tifoide Policlinico (sez prat 44 1937 100 [illegible] 37

[illegible] Pelisse, R and Bat... P Typhoid With Buccal Ulcerations and Terminal Hematemesis in Child Years Old Marseille-méd 2: 602-605 1930

[illegible] Fraser W M Glover B T J and Glass, V Epidemic of Paratyphoid B Fever in Liverpool and District Brit M J 2: 369-371 1937

metastases which contain bacilli sometimes even when the blood culture fails to demonstrate them. The pathology of the inflammatory reaction is similar to that of typhoid [364]

Brucellosis (Undulant Fever)

Brucellosis (undulant fever) is a mild septicemia caused by bacteria of the genus Brucella which includes several pathogenic varieties. *Brucella melitensis* (Bruce) is found in goats, *Brucella abortus* (Bang) in cattle and *Brucella suis* (Traum) in swine. The microorganisms are very small pleomorphic, gram negative nonmotile bacteria which are pathogenic for guinea pigs The infection from goats is also known as Mediterranean or Malta fever the infection from cattle as Bang s disease.

The routes of infection in man are the gastrointestinal tract and the skin. The incubation period varies from ten days to three weeks.[365] The onset is gradual and the course of the fever varies Most characteristic is the undulant type with repeated periods of persistingly high temperature of ten to twenty days in duration The general condition remains good the paucity of objective signs is a remarkable clinical feature [366-367]

The disease is rarely fatal but a great number of complications are known They include heart and lung manifestations, arthritis neuritis meningitis encephalitis orchitis mastitis abortion and others The laboratory diagnosis is based on agglutination blood cultures which need two weeks to grow and skin tests with brucella vaccines which are more reliable than serum agglutination [368] The cutaneous reactions can be used for differentiation of the various types.

Dermadromes —Skin manifestations are either ectogenous or hematogenous. The former occur at the site of *contact with infectious material* particularly on the hands and forearms of veterinarians after delivery or manual removal of the placenta of Bang infected cows. These persons, as a rule do not have a general Bang infection They seem to become silently sensitized by repeated contacts Thirty per cent of 325 Danish veterinarians [369] 10 per cent of the Swiss [370] and 20 per cent of fifty veterinarians from Michigan[371] suffered from this allergy In some cases warmth or itching and urticaria are felt during or very shortly after the contact While this early reaction may be caused by other substances in the cattle serum or placenta [367 372] a second type of eruption a

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[364] Fraenkel E Ueber Roseola paratyphosa, Ztschr f Hy Infektionsk 93 372-388, 1921

[365] Hardy A V Jordan, C F and Borts, I H Undulant Fever Nat I st Health Bull N 158 pp 89 1931

[366] Robinson F H and Evans A C Chronic Brucellosis, J A M A 113 201 206 1939

[367] Huddleson J F Brucellosis in Man and Animals, New York, 1943 Commonwealth Fund

[368] Huddleson J F The Diagnosis and Control of Brucellosis, J Oklahoma M A 35 106-111 1942

[369] Harthausen, H and Thomsen, A Brucella-Ausschlag bei Tierärzten Ein eigentümliche professionelle Hautaffection wahrscheinlich allergischer Natur hervorgerufen on Bacillus abortus (Bang) Arch f Dermat & Syph 163 477-491 1931

[370] Stehoch A Skin Lesions in Brucellosis Praxis 32 581-584, 1943

[371] Huddleson I F and Johnson, H W Brucellosis I The Significance f Brucella Agglutinins in the Blood f Veterinarians, J A M A 94 1905-1907 1930

[372] Jadassohn, W Brucella Bang-Ausschlag und Urticaria bei Tierärzten Zbl 44 320

papulopustular folliculitis which develops within two days, is generally considered to be a specific reaction to *Brucella abortus* (Bang) The eruption is described by Huddleson[387] as consisting of small discrete elevated, reddish widely separated follicular papules from 2 to 5 mm in diameter and 1 to 2 mm in elevation The rash itches or burns intensely and may last as long as three or four weeks. Occasionally deep necrotic tuberculid-like lesions or erythema exudativum multiforme-resembling forms are seen Erythema brucellum as the condition has been termed by Huddleson and Johnson [illegible] is rarely followed by general brucellosis (Dietel and others after W Jadassohn[illegible]) In some of the sensitized persons the attacks seem to become more acute with renewed exposures.[illegible]

The systemic infection infrequently (11 per cent[illegible]) produces rashes. Their incidence seems to differ in various countries. They have been described as macular as resembling the roseola in typhoid[illegible] (Curschmann after W Jadassohn) as star-shaped vividly red or purple spots on the forearms neck and face in porcine cases [illegible] morbilliform [illegible] scarlatiniform[illegible] (Grocco after Lustig and Vernoni) erythema exudativum multiforme-like,[illegible] as papular rashes involving cheeks, neck and extensor surfaces,[illegible] hemorrhagic bullous [illegible] varicelliform [illegible] and as resembling dermatitis herpetiformis and lasting over three years.[illegible] The appearance in crops and the evanescent character of the rash are often emphasized. Aphthae in the mouth and a bad taste are sometimes noted early Tonsillitis vesiculosa and uvulitis have been described.[illegible] Ulcus vulvae acutum occurs as a complication as it does in typhoid fever [illegible]

Gabbi[illegible] tried to *differentiate* the dermadromes of morbus Bruce (Malta fever) and morbus Bang In the former he found the rash more often scarlatiniform in the latter more frequently vesicular and accompanied by bromidrosis. Profuse and exhausting sweats are one of the most unpleasant features of brucellosis [387] Sudamina, maceration and desquamation often follow the sweats.[illegible]

I I was almost no rashes have been observed in large number of cases. (Personal communication to the author from Dr Borts and Dr Jordan, Des Moines, Iowa.)

[illegible] Citron H Brucella-Ausschlag bei Tierärzten, Meilern, Zbl [illegible] 343, [illegible]

[illegible] Bahmer K Bang-Infektion des Menschen, Ergebn d Hyg Bakt Immunitätsforsch exper Therap 13 485-518, 1932

[illegible] Kämmerling, J Bang' Disease in Man, Ztschr f. klin, Fortschr [illegible] 440-443, [illegible]

[illegible] Löffler W Febris undulans Bang des Menschen, Leipzig, 1930, Curt Kabitzsch

[illegible] Vogel, W Uebertragung der Banginfektion vom Schwein auf den Menschen, Schweiz med. Wchnschr 61 970-978, 1931

[illegible] Rimbaud L Janbon, M and Alquié, R Undulant Fever—Generalized Vesiculous Erythema in Melitococcosis, Arch Soc d sc méd. et. biol de Montpellier [illegible] 1937

[illegible] Lustig, A and Vernoni, G Maltafieber Kolle Kraus, Uhlenhuth, Handbuch der pathogenen Mikroorganismen, Berlin, 1930, Gustav Fischer and Urban & Schwarzenberg, pp 311-[illegible]

[illegible] Arakelov J Das Maltafieber in Aserbaidschan, Venerol [illegible]

[illegible] Custer H Bang-Infektion des Menschen, Schweiz. med. Wchnschr 1 [illegible], 1933, Zbl [illegible]

[illegible] Sakharevsky W N and Karbashevsky J A Ueber Bangfieber beim Menschen, Deutsche tierärztl Wchnschr [illegible] 369-372, 1930 Zbl [illegible]

[illegible] Zoman, E. Haut und Nervenerscheinungen bei Morbus Bang, [illegible] 1930 Zbl 64 84

[illegible] Urbach, E Food Infection (Bacillus Bang) Wien, klin Wchnschr [illegible] 144-147

[illegible] Harbet, L Diagnosis of Otorhinolaryngologic Conditions due to Undulant Fever [illegible] 1938 C Ohrenh 71 1152-1160 1937

[illegible] Katzenellenbogen, I Ulcus Vulvae Acutum (Lipschütz) Following Malta Fever Monatschr A in, Palestine, 1940, Harefuah

[illegible] Gabbi U Morbus Bruce Morbus Bang, Giorn di clin med 11 [illegible] Zbl 44 84

[illegible] Paterson, D H and Hardwick, C Undulant Fever in Children, Arch Dis Childhood [illegible] 63-65 1938

Only few histological examinations of the lesions have been made and they refer to the contact eruptions or to cutaneous reactions with *Brucella melitensis* allergen. Perifollicular and perivascular infiltration with lymphocytes leukocytes, and monocytes and occasionally an abscess have been observed [illegible]

Plague

In bubonic plague the primary skin lesion is caused by the bite of an infected rat flea. It may remain small and painless or it may develop into a pustule or even into a carbuncle followed by large suppurating bubos and septicemia In the pulmonary form of plague a rapidly fatal septicemia follows or accompanies the severe pneumonia. The exciting organism is *Pasteurella pestis* which is found in the blood the sputum the urine and in many lesions especially in the bubonic pus. No other bacillus is known to occur in bubos in such large numbers.[illegible]

The disease is prevalent among several rodents. Occasional cases or small epidemics have often been seen in the western and southern United States. The data on the mortality and the value of serum and other treatment are extremely divergent. In many epidemics the mortality was higher than 80 per cent.

Dermadromes.—Hemorrhagic inflammation is a characteristic feature of the infection This is particularly true of the *plague carbuncle* which otherwise does not differ very much from any other carbuncle. The plague carbuncle starts as a small infiltrate with one or several blisters on its surface. These blisters may coalesce into a bulla with seropurulent and often hemorrhagic contents in which plague bacilli abound. The bleb disappears fast, leaving a deep necrotic ulcer with raised edges on top of a rapidly growing cellulitis. A lymphangitic streak, sometimes with bubonuli connects the carbuncle with the regional lymph nodes which turn into *bubos* The development of the carbuncle may become arrested in any stage leaving hard cutaneous infiltrates which abound in bacilli and are known as *plague boils*

The plague carbuncle is only occasionally the primary lesion of the plague infection More often the carbuncle is a metastatic, hematogenous or lymphogenous infection [illegible] Sometimes the carbuncle develops at the site of infection at a later time than the bubo The incidence of carbuncles varies in the epidemics from 10 to 15 per cent being a fair average [illegible] Araujo[illegible] in a recent report found skin manifestations in only 7 per cent. Other skin manifestations are erythema pustules vesicles, bullae and hemorrhagic lesions. The latter are supposed to be so common and their appearance so ominous that from them originated the name of black death as the disease was called during the great European outbreaks in the Middle Ages. Such large fulminant hemorrhagic skin lesions have

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[illegible] Gersh I and Black W C Histology of Cutaneous Reactions to Brucella Melitensis Antigen. Arch Path 27 307-312, 1939

[illegible] Lloyd, B J Personal Experiences With Bubonic Plague J Trop Med 44 119-123, 1941

[illegible] Müller H F and Pöch, R Die Pest, Nothnagel' Specielle Pathologie und Therapie Vienna, 1900 Alfred Hölder

[illegible] Araujo E Hauterscheinungen bei Pest Statistisches, Klinisches, Pathogenetisches, Bresil-med 35 1-4 1921 Abt 4 152

not been noticed in the large plague epidemics of modern times. However petechial rashes occur which contain bacilli and therefore are a true metastatic infection (Albrecht and Ghon after Müller and Pöch [391]) Hemorrhagic streaks around the navel and in other sites have been recorded [392]

A rare occurrence are the papulopustular generalized dense varioliform exanthems.[393]

Tularemia

Tularemia is named after the California county of Tulare where it was first observed among squirrels by McCoy [394] In man it is usually acquired by the handling especially skinning of wild rabbits, hares squirrels and other rodents, or by eating the insufficiently cooked meat from them. It has been shown to be carried by ticks [395-396] bedbugs [397] and other insects.[398] Laboratory infections have occurred in a considerable number although no contagion from man to man has become known except for one case of a physician at an autopsy (Weilbacher and Moss after Robert[399])

The cause is a small pleomorphic gram-negative bacterium, *Pasteurella tularensis* which seems to be able to penetrate the unbroken skin as well as the mucosa. The incubation period is most often four days but it varies considerably In traumatic infections the first symptoms at the site of the injury may develop after a few hours.[400-401] Fever may break out suddenly before any other symptoms even before the primary lesion appears.[402] This indicates the early dissemination of the infection If the infection begins in the skin which is by far the most common way a primary lesion develops and the disease spreads along the lymphatics. The regional lymphatic vessels become indurated small nodules or bubonuli appear along them and bubos develop which may reach large size and may suppurate.

If the infection occurs in the conjunctival sac (1 per cent Hurst after Tassman[403] 3 per cent after Pullen and Stuart[400] 12 per cent Vrla after Robert[399]) or in the tonsils characteristic clinical pictures of long-lasting lid edema and suppurative lymphadenitis develop The typhoid-resembling type, without apparent portal of infection is very rare. It has been seen in several laboratory infections. The severity of the infection varies from mild ambulatory cases with little fever and no internal complications to illnesses of many months duration sometimes with a fatal outcome. The mortality in the United States amounted

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[393] Teissier P Reilly J Cambessédès, and Cathala Formes exanthématiques de la peste bubonique Bull et mém Soc méd d hôp. d Par 49: 824-831 1925

[394] McCoy G W and Chapin C W Tularemia Bull 43 Hyg Lab U S P H S 1911

[395] Davis G E Philip, C B. and Parker R R Isolation From the Rocky Mountain Wood Tick of Bacterium Tularense Am J H 19: 449-456, 1934

[396] Byfield, G V Breslow L Crum, R R J and Hershey N J Tick Borne Tularemia, J A M A 137 191 198, 1948

[397] Bogdanko V Bedbugs as Carriers of Tularemia, Vestnik mikr 14 436 1935 Zbl 91 311

[398] Miller H E and Tassola, L R Tularemia, Arch. Derm & Syph. 19: 876-380, 1929

[399] Robert, F Tularemia Review of Literature Dermatologica 60: 98-107 1930

[400] Pullen, R L and Stuart, B M Tularemia, 225 Cases, J A M.A. 129 495-500, 1945

[401] Stuart, B M Tularemia and Pneumonia Am J M Sc 201 232, 1944

[402] Das, K. O Die Bubonenformen der Tularämie Zentralbl f Chir 67 1218-1231, 1940

[403] Tassman, J S. Eye Manifestations of Internal Diseases, St Louis, 1942, The C V Mosby Company

to 4 8 per cent among 7 077 cases reported from 1924 to 1936 [304] The autopsy findings often resembled those of tuberculosis.[303,305] There are miliary gray foci in the enlarged spleen and less often in the liver and in the lungs, which may show pneumonia or abscess The microscopic picture of the lymph nodes and the subcutaneous nodules is that of an infectious granuloma[306] with epithelioid cells lymphocytes and giant cells of the Langhans type creating a great similarity to tuberculosis.[307]

The microorganism can be isolated from the blood of the patient by inoculation into guinea pigs and by culture This however is hardly possible after the first two weeks[308] and it has rarely been accomplished from an open lesion [309] Agglutination in serum dilutions above 1:80 is considered diagnostic.[31] Skin allergy to tularemia[311] develops as early as four days after infection or even sooner [312] The intracutaneous test with 0 02 or 0 05 c.c. of a bacterial suspension is read after forty-eight hours The disease seems to leave the patients immune

The treatment is symptomatic. The value of antiserum derived from goats [313] which has been found effective in reducing the severity and duration of the disease [306] needs confirmation The beneficial effect of the sulfonamides is not generally confirmed [314] Streptomycin is now considered to be the drug of choice

Dermadromes.—The primary lesion may occur almost anywhere on the skin It may be single or there may be multiple lesions. The primary lesion appears after a period of about one week when general dissemination has already manifested itself by fever and malaise. Even the regional lymph nodes may become enlarged and tender before the appearance of the primary lesion The initial lesion is a papule the center of which soon becomes depressed and necrotic, forming a punched-out ulcer with raised edges. This ulcer is painful and defies therapy but after several weeks it heals spontaneously [306] The early lesions of tularemia may imitate syphilis anthrax, felon or other conditions. Due to the lymphatic chain of nodules or abscesses the picture may closely resemble sporotrichosis or primary inoculation tuberculosis.[308,315]

In the primary stage the diagnosis often can be secured only by the intracutaneous test

The bubonuli and lymph nodes may become tender adhere to the skin and ulcerate In one case reported by Blackford and Smith (quoted after Hitch

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[304] Cumming H S Tularemia, Bull Office Internat d hyg Pub 29 2532 1937
[305] Gundry L P and Warner C G Fatal Tularemia 15 Autopsies, Ann Int Med 7 837-852 1934
[306] Lawless, J K Tularemia, Arch Derma & Syph 44 147 160 1941
[307] G W H and Jacob F M Tularemia Arch Dermat & Syph 21 900, 1931
[308] Hitch, T M and Smith, D C Cutaneous Manifestations of Tularemia, Arch Dermat & Syph 39 859-876 1938
[309] Netherton E W Tularemia Cutaneous Manifestations, Arch Dermat & Syph 16 170-1 4 1927
[310] Pasternack J G Tularemic Inguinal Buboes F Dog Tick Bites J A M A 112 1814-1817 1939
Foshay L Tularemia Earlier Diagnosis by Intradermal Reaction, J Infect Dis 51 286, 1932
[312] Parson G W Interesting Cases of Tularemia, Tri-State M J 13 2709-2714 1941
[313] Foshay L Tularemia Treated by New Specific Antiserum Am J M Sc 187 235-246 1934
[314] Werlin, E H Tularemia, 10 Cases J Oklahoma M A 35 103-106 1942
[315] Chelmire B Tularemia Resembling Sporotrichosis, Arch Dermat & Syph 19 918-931 1929

and Smith[443]) fungating growths developed out of such bubonuli. The histological structure of the subcutaneous nodules is definitely tuberculoid.

Generalized *eruptions* are a feature of the disease but they occur only in a fraction of the cases (8 per cent after Pullen and Stuart[444]) and are not characterized by any specific morphology. Hitch and Smith[443] surveyed forty-eight cases of secondary eruption in tularemia. They demonstrated that eruptions occur in all types of the disease, most often in the second week, and that the average duration is three weeks. However, great deviation of the average figures is

Fig. 3.—Tularemia. Erythema exudativum multiforme resembling eruption on fifteenth day of the disease. (From Hitch, J. M., and Smith, Dudley C.: Arch. Dermat., 1938.)



Fig. 3a.—Tularemia. Papular rash. (Courtesy Dr. Walter M. Simpson, from Sutton and Sutton, Diseases of the Skin, The C. V. Mosby Company.)

frequently observed. Pleomorphism is a characteristic feature. The most commonly encountered morphologic type was the *papular* eruption which was seen in approximately one half of the eruptive cases. Less common are maculas, pustules, vesicles, wheals, nodules, ulcerations and transitional forms. The rashes often gave the impression of erythema multiforme, sometimes with herpes iris lesions. The eruptions were generalized or they involved only a part of the body, mostly the upper trunk and the arms, especially on the side of the primary lesion. In ophthalmic cases a facial eruption appeared on the side of the infected eye. The eruptive cases did not differ from the noneruptive ones with regard to incubation period or agglutination titer. The histological examination did not reveal changes other than one might expect, that is, edema and perivascular lymphocytic and fibroblastic infiltration. The common appearance of the rashes after the period of bacteremia and fever supports the conception of the toxic rather than infectious nature of the secondary rashes in tularemia.

The prognosis of the secondary rashes is good; the treatment is symptomatic.



Fig. 37.—Primary lesion of tularemia and lymphangitis [illegible] weeks after onset. (Courtesy Dr. Walter M. Simpson; from Sutton and Sutton, Diseases of the Skin, The C. V. Mosby Company.)

Erythema Arthriticum Epidemicum, Ratbite Fever or Haverhill Fever

Erythema arthriticum epidemicum, ratbite fever, Haverhill fever*—none of these three names is correct. The disease is not always epidemic, does not always follow a rat bite, and Haverhill, Mass., is neither the only nor the first place where it was observed. Erythema arthriticum would be a good name, but the term Haverhill fever has become established.

The disease is an acute infection which usually follows a rat bite. It should not be confused with sodoku which is also transmitted by rat bites. While the ratbite cases occur sporadically,[98] a milk-borne epidemic with eighty-six cases

* For bibliography of the ratbite fevers, see Brown, T. M., and Nunemaker, J. C.: Bull. Johns Hopkins Hosp. 70: 201-301, 19[illegible]2.

[98] Farrell, E., Lordi, G. H., and Vogel, J.: Haverhill Fever: Case With Review of Literature, Arch. Int. Med. 64: [illegible]14, 1939.

was observed in Haverhill Mass in 1926[11] [11] and another milk borne—not quite verified—outbreak of 600 cases at Chester Pa. (Armstrong and H Wood after Place and Sutton[118]) The epidemic and sporadic forms are caused by the nonmotile pleomorphic gram negative and nonacid-fast *Streptobacillus monili formis* (Haverhillia multiformis)[119] which during the fever can be cultured from the blood of the patient. Mice die from the disease forty-eight hours after intra peritoneal injection of blood

About three days after the infecting bite of rats, who often harbor the microorganism in their pharynx, the disease starts quite suddenly with malaise headache chill and high fever A rash and acute polyarthritis develop early and heal after several days. There is a leukocytosis of over 12 000 The spleen is not enlarged. There were no fatalities in the Haverhill epidemic. A *rash* was observed in 94 per cent of the Haverhill cases which appeared during the first week, most often between the second and fifth days It involved predomi nantly the lateral and distal extensor surfaces of the extremities rarely the trunk and face. There is sometimes accentuation around the joints.[11] The exanthem has been described as a maculopapular rubelliform or morbilliform vividly red eruption with the efflorescences being about 3 to 5 mm in size.[119] In some cases the exanthem had the characteristics of erythema exudativum multiforme (Levaditi Nicolau and Poincloux after Farrel and associates[118]) The rash usually fades after one week, with little desquamation or pigmentation The exanthem may reappear with new paroxysms of the fever Then it is likely to be more confluent.[119] A *hemorrhagic tendency* can be demonstrated by a positive tourniquet test and by pin point hemorrhages in the center of the lesions.

In the cases studied by Allbritten Sheely and Teffers,[120] tender purpuric nodules with yellow nonsuppurative, depressed centers, resembling those seen in subacute bacterial endocarditis, appeared around the finger tips They proba bly are metastatic embolic foci. Lymphadenopathy in relation to the site of the bite is rare.[120]

The *diagnosis* rests on the history of a rat bite and the laboratory findings Agglutination tests are known A cutaneous reaction to suspensions of killed streptobacilli was present in 83 per cent of the Haverhill patients tested late in convalescence. It seems important to compare the symptomatology of Haver hill fever and that of sodoku, the other ratbite disease, which may occasionally cause a syndrome quite indistinguishable from Haverhill fever[121] Usually sodoku (see under sodoku) presents a chancriform induration at the bitten area which is followed by lymphangitis. Arthritis is rare The causative organisms of both diseases are penicill n sensitive (Wheeler after Pleming[122])

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[11] Place E. H Sutton, L E and Willner O Erythema Arthriticum Epidemicum Preliminary Report, Boston M & S J 194 285-287 1926

[118] Place E H and Sutton L E Haverhill Fever Arch I t Med 54 659 1934

[119] Parker F J and Hudson N P Haverhill Fever Am J Path 2 357 1926

[120] Allbritten F F Sheely R F and Jeffers W A Haverhillia Multiformis Septicemia Rela tionship to Haverhill and Rat-bite Fevers J A M A 114 2360-2363 1940

[121] Brown T M and Nunemaker J C Rat-bite Fever Review of American Cases, Bull. J hns Hopkins Hosp 70 201 942

Glanders (Malleus)

Glanders (malleus) occurs predominantly and in large epizootics among horses from which most of the rare human cases originate A number of laboratory infections have become known [221] The disease which has an incubation period of from three to five days is caused by the pleomorphic nonmotile bacillus *Malleomyces mallei* The germ enters the human body through the skin or through the mucosa possibly without a wound. From a primary lesion the disease spreads and frequently becomes generalized taking an acute or irregularly relapsing chronic course of unfavorable prognosis Specific lesions may occur in any organ but there is a definite cutaneous and mucosal affinity The predominantly lymphangitic form is sometimes called farcy while the term glanders is often used for those cases in which the mucosal especially the rhinitic involvement dominates the picture Not very long ago the two forms were believed to be different entities. The specific malleus lesions are granulomas which resemble tuberculosis in many ways.

The *diagnosis* rests on a history of contact with horses or mules the unusual clinical picture the microscopic and cultural evidence of *Malleomyces mallei* the intraperitoneal inoculation into the male guinea pig followed by the specific inflammation of the testes and various serological and allergic tests among which the complement fixation the ophthalmic and the intracutaneous tests have been used in man

Dermadromes.—The primary lesion which has been most often observed on the hands and arms the face and the conjunctiva is a furuncle-like infiltration which soon breaks down in the center and forms an ulcer with jagged raised livid and infiltrated edges and a necrotic floor with edematous and erythematous surroundings.[222] The lesion may reach dollar size but it finally heals spontaneously In some cases it fails to develop so that lymphangitis appears as the first cutaneous symptom Lymphangitis without noticeable lymphadenitis is a peculiar feature of malleus in human beings.[222] The wire or pencil like lymphatics are palpable along the extremity and small bubonuli (buds) develop alongside the vessels. This type of lymphangitis resembles sporotrichosis or tuberculosis Sinuses, sievel ke perforations ulcers and scars may develop In rare instances the disease becomes chronic in this stage The primary lesion of the oral or nasal mucosa is an ulcer similar to that of the skin

General *systemic* infection follows the majority of the primary lesions. The period after which systemic symptoms appear may be a few days to many weeks or months. The skin manifestations of the systemic infection have a predilection for the nose and face These secondary malleids appear in crops and show great differences in severity grouping and number The exanthem usually starts as a *roseola* The maculae which in rare instances are purpuric, become papular papulopustular and later ulcerative They are occasionally bullous or composed

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[221]Roeloff J W Acut Glanders Case Nederl tijdschr geneesk 73 [illegible] 1929 Zbl [illegible]
[222]Bierbaum K and Gottron H Rotz (Malleus) Handb d H u G k [illegible] 1929

of concentric rings[illegible] resembling erythema multiforme. These ulcers may by infiltration of the surroundings and by coalescence grow to larger plaques which may also develop from cutaneous or subcutaneous nodules. Breaking down of nodules or plaques may cause deep destruction of the muscles and tendons and even affect the joints.[illegible] Destructive and suppurative lesions in and around the nose may cause a peculiar swelling and erythema of the nose which has been termed by de Balogh [illegible] who reported eight cases, potato nose. This author describes nonsuppurative livid nodules in the face as typical secondary lesions.

The *histology* of the fully developed lesions shows granulation tissue composed predominantly of leukocytes and to a lesser degree of epithelioid plasma and mast cells. There is a pronounced necrotic tendency Karyorrhexis is a feature and bacilli may occur in large numbers

Sporotrichosis tuberculosis and pyogenic lymphangitis must be considered in the lymphangitic period and syphilis and mycosis fungoides in the later systemic stages. The common concentration around the nose and the necrotic tendency of the granuloma support the clinical diagnosis of malleus. However considering the rarity of human glanders and the many varieties of its course all laboratory methods must be employed

Generalized glanders in man is, almost without exception a fatal disease Chronic localized malleus heals spontaneously in about 50 per cent of the cases (Bollinger after Bierbaum and Gottron[illegible]) No specific treatment is known

Cholera Asiatica

Cholera asiatica is an acute often epidemic, infection caused by the *Vibrio comma* (Koch) In its severest fulminating form the disease may run a fatal course in from three to fou hours but less severe forms are well known The outstanding symptoms are excessive watery diarrhea dehydration and circulatory collapse.

Dermadromes —The ski is described as pale or cyanotic even livid covered with sweat wrinkled and withered. Urea frost has often been seen covering such dehydrated patients. In fact this sign was described in cholera long before its association with uremia was noted (Schottin after Chargin and Keil[illegible]) In cholera there is a pronounced tendency to necroses and decubiti.[illegible] Exanthems are infrequent.

The older literature contains a number of references. Liebermeister [illegible] in a monograph written after the great epidemic of 17 000 cases in Hamburg Germany in 1892 denied the existence of a specific exanthem at the height of the disease In the early stages of recovery cyanotic spots may remain as remnants

[illegible]Leszinsky A Ueber einen Fall [illegible] Rotz, Bruns Beitr z klin Chir 128 [illegible] 1923

[illegible]Balogh E de [illegible] Lesions in Human Glanders, Verh 9 Internat Kongr Dermat. 2: 427–431 1936

[illegible]Chargin L and Keil H Skin Diseases in Nonsurgical Renal Disease Arch. Dermat. & Syph. 26 314-338 1932

[illegible]Kisch H and Doerr R Cholera Asiatica. Handbuch der inneren Medizin, Berlin, 1925, Julius Springer

[illegible]Liebermeister G Cholera Asiatica and Cholera nostras, Nothnagel Specielle Pathologie und Therapie Vienna. 1896 Alfred Hölder

of the collapse of circulation during the attack. Roseola and other erythemas especially of the erythema multiforme type papules vesicles urticaria and petechiae have occasionally been seen but the specific character of these rashes has not been demonstrated Some may have been drug eruptions [237]

Whooping Cough

During the characteristic attacks the glottis is temporarily closed and at the termination of the spell it is opened for a long-drawn crowing inspiration.[238] The disease is caused by a small bacillus with accentuated poles discovered by Bordet and Gengou

Dermadromes —The repeated severe coughing spells frequently produce some puffiness around the eyes especially of the upper lids together with slight chemosis This is known as the *whooping cough face* *Petechiae* which are quite rare in the skin occur more frequently in the mucosae especially in the conjunctivae of young children Both bulbar *conjunctivae may be deep red* a terrifying but harmless sign

The vesicles of a *varicella exanthem* coinciding with whooping cough may *become hemorrhagic* due to the coughing bouts This is especially true of the vesicles in the area drained by the upper vena cava [239] The violent fluctuations of vascular pressure during the cough and possibly the infectious and toxic damage to the capillaries may prepare the rhexis of the capillaries

Cutaneous *emphysema* is a rare but dangerous complication of whooping cough It is caused by the rupture of alveolar vesicles due to the high intra pulmonary pressure. From the ruptured lung the air is pressed under the pleura which on autopsy has been seen to be separated from the lung The air follows the mediastinum and finally reaches the skin of the neck or chest.

A well known complication of whooping cough is the shallow *ulceration of the frenulum linguae* It results from injury and irritation of the frenulum caused during the coughing by the incisor teeth or in the absence of teeth by the hard lower jaw

Diphtheria

Exanthems indicative of generalized diphtheric infection are rare. Some rashes have been interpreted as initial exanthems since they occurred during the first day [240]

Purpuric, morbilliform, scarlatiniform, papular and vesicular *eruptions* resembling erythema nodosum and multiforme, and even typhoidlike rose spots have been described Allowance must be made for drug eruptions, true scarlet fever [241] and serum exanthems.

Herpes seems to be rarer than in many other infectious diseases. The herpes vesicles may contain bacilli (Rall after Biberstein[240])

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[238] Knoepfelmacher W Whooping Cough Pfaundler and Schlossmann The Diseases of Children, vol III Philadelphia, 1935 J B Lippincott Company pp 330-351

[240] Biberstein, H Die Diphtherie der Haut, Handb d H Gk 9, 1 146-182 1929

[241] Bruno, P Esantemi scarlattiniformi sieroterapia nel corso della difteri Scritti med dedicati Carlo Comba Riv di clin pediat 27 426-438, 1929

Panniculitis (Weber-Christian Disease)

Twenty-eight cases of a syndrome of relapsing febrile, nodular nonsuppurative panniculitis (Weber-Christian disease) have been reported since 1892 [illegible]. There are crops of cutaneous and subcutaneous painless or tender nodules, mostly on the thighs and arms but also on the trunk, and accompanied by fever. The lesions are the expression of an inflammatory process which results in atrophy of the subcutaneous fat producing in the skin lasting depressions of a varying depth and width. Fever is a constant symptom. Two cases were fatal. The etiology and even the clinical entity itself are still controversial. Focal infection, tuberculosis, eruptions from iodine or bromides, and other causes have been considered [illegible].

[illegible] Pfeifer, V. Ueber einen Fall von hochgradiger Atrophie des subcutanen Fettgewebes, Deutsches Arch. f. klin. Med. 50: 438-449, 1892.

[illegible] Larkin, V. P., De Sanctis, A. G., and Margulis, A. R. Panniculitis—Review of Literature. Am. J. Dis. Child 67: 120-125, 1944.

Chapter IV

SYSTEMIC INFECTIONS

Influenza

Influenza is almost certainly caused by at least three different types of virus[334] now called A B and V but is usually complicated by the secondary invasion of various bacilli especially the Pfeiffer bacillus the pneumococcus and the pyogenic cocci Sporadic cases occur although epidemics and pandemics are characteristic of the disease. Influenza is very contagious The incubation period is short about two days. The onset is quite sudden sometimes with marked catarrhal symptoms or sore throat. The fever is irregular and chills and remissions are common The respiratory tract in its full length is inflamed *bronchitis and pneumonia are serious complications which in 1918 caused most* of the deaths[83] Prostration is often marked and not explained by the temperature alone Gastrointestinal symptoms and sometimes severe and irreversible lesions of the nervous system may in a small minority of cases dominate the picture. Many other complications are known Mild leukopenia is common before secondary infection supervenes.

The post mortem findings concern chiefly the respiratory tract

The mortality varies from 15 to 60 per cent depending on the character of the epidemic[335] although exact figures are not available In 1918-1919 at the time of the last influenza pandemic there were 550 000 deaths in the United States in excess of the normal expectancy No specific treatment has been discovered as yet

Dermadromes—The skin manifestations are neither impressive nor of diagnostic importance They rarely influence the course or cause suffering to the patient[336] *The incidence of skin and oral symptoms given by various authors* varies from 1 to 20 per cent. However such percentages are of little value in a disease which in many cases is difficult to differentiate from other common respiratory infections.

During the febrile period ***herpes*** simplex is common and sometimes develops even after the temperature has returned to normal The appearance of herpes does not seem to depend on the respiratory in olvement.[337]

Exanthems of great variability have often been noticed usually in the early stages of the infection These skin eruptions are most often macular[338] or mor

[334]Horsfall F L J Present Status of Influenza J A M A 120 284 287 1942

[335]Top F H Communicable Diseases St Louis 1941 The C V Mosby Company

[336]Schütz, H Dermatologie und Grippe Med Welt 13 1506-1510 1939

[337]Schumacher C and Mosocorpa, C Haut- und Schleimhaut erkrankungen bei Grippe Zbl 16 259-264 1925

[338]Freund Grippeexantheme Zbl 23 628.

billiform [339] less frequently scarlatiniform.[340] Besides these main types, urticarial, vivid red papular [341] purpuric, and spotted typhuslike rashes have been recorded. There are combinations of macular and hemorrhagic lesions.[342] The serious prognostic significance of purpuric rashes is often emphasized. Erythema nodosum and erythema exudativum multiforme[343] have been observed in a considerable number of cases.

Most of the influenza rashes are very transitory [337,344] The difficulty in differentiation from measles scarlet fever and other exanthematic diseases is often great. A carefully taken history of contacts and previous diseases consideration of the incubation period and negative results of the diagnostic procedures used in other infections will usually help to overcome the difficulties In sporadic cases the diagnosis may be made only after further observation of the course Jordan[344] emphasizes the lack of adenopathy as a criterion against rubella.



Fig 28.—Virus tongue in influenza. The tongue is large, flabby and shows dental impressions. (Courtesy Dr Max Fox)

In the *oral* mucosa circumscribed erythema of the soft palate and the posterior tongue and a buccal exanthem not unlike Koplik s spots in measles are common [337] A flabby slightly edematous tongue showing marginal impressions of the teeth (virus tongue) is often considered characteristic of influenza and other virus diseases. The pharyngeal involvement may occasionally become severe. Follicular tonsillitis pseudomembranes of the pharynx and small ulcerations of the mucosa may even lead to glottic edema

[339] Opitz H Grippe [illegible] Kinderärztl. Praxis 6 154-156 1935.
[340] Koch, H Exanthem bei grippalen Erkrankungen, Wien med Wchnschr [illegible] 1932.
[341] Desy G Sulle manifestazioni papulari cutanee nella influenza, Riform med [illegible] 1937
[342] Leichtentritt, B and Schober W Grippeexantheme Klin Wchnschr [illegible] 1934
[343] Oppenheim Grippeexantheme Zbl [illegible] 743
[344] Jordan, A Ueber Grippeausschläge Dermat Wchnschr [illegible] 1011 1014, [illegible].

Following the acute period erysipelas of the face has often been observed especially in the older epidemics. Other common cutaneous sequelae are furunculosis and herpes zoster Symmetric gangrene of the extremities is an exceedingly rare event.[245]

Alopecia diffusa was a common dermadrome during the epidemic of 1918 The shedding of the hair after influenza was often troublesome although the hair usually grew back. Beau s lines of the nails were often observed The dermadromes of influenzal encephalitis will be discussed in Chapter XXXIX

Measles

It is generally agreed that measles is caused by a filtrable virus which lately has been cultured in the chick embryo[247] (Kunert and Wenkebach after Rietschel[246] and successfully inoculated into the child after several passages.



Fig. 30 —Measles, fifth day Exanthem and conjunctivitis. (Courtesy Dr M Fox)

The disease is highly contagious among persons who have not had much exposure to the virus and therefore, is predominantly a child s disease Measles

[245] Mott, A Gangrène aiguë symétrique des extrémités post-grippale Gaz méd de France 46 649-650 1939

[246] Rietschel, H Measles, Review of Literature Monatschr f Kinderh 80 313-354 1911

[247] Rake G and Schaffer M F Studies of Measles Use of Chorio-Allantois of Developing Chicken Embryo J Immunol. 38 177 1940.

is most contagious about twenty four hours before the eruption. With the appearance of the exanthem the infectivity decreases rapidly and is nil at the time of desquamation. The infectious agent is present in the respiratory tract and in the blood and it has also been demonstrated in artificial blisters of the skin Lifelong specific immunity after measles is the rule true reinfection being extremely rare.

The first catarrhal symptoms appear not too suddenly after an incubation period of about ten days. Headache, anorexia conjunctivitis and coryza sometimes with nosebleed cough vomiting and sudden fever are the common prodromal symptoms. On the first day the lower lids may be slightly puffy and a fairly definite erythematous transverse line appears across the conjunctival surface of the lower eyelid about a third of the distance from the lid margin to the fornix (Stimson after Sobel in Mackee and Cipollaro [44])

On the second day of the prodromal stage a few (from six to twenty) pin point sized white spots often surrounded by a bright red at first narrow but soon widening areola appear on the buccal and later often on the labial mucosa. This prodromal mucosal eruption which is commonly known as Koplik's spots is of great diagnostic importance since it hardly occurs in other diseases and it can be seen in about 90 per cent of the measles cases, preceding the outbreak of the exanthem The Koplik spots vanish when the rash appears and are soon followed by an enanthem of dark red spots of pin head to lentil size which may coalesce into large spots scattered over the soft palate and later over greater areas. Koplik's spots may be absent in the measles of small children.[141]

The temperature usually drops on the second day only to rise again during the next two days. Between the third and fifth days (two weeks after the infection) the rash appears. The disease reaches its height around the fifth day and from that time on the symptoms are eased On the seventh or eighth day after the full development of the rash the temperature gradually becomes normal the rash fades, and the catarrhal symptoms are no longer annoying Recovery follows gradually Cervical adenopathy is common but is mild and rarely leads to abscesses.

The clinical picture is dominated by the rash and the intense catarrhal involvement of the mucous membranes, particularly of the respiratory tract and of the eyes. There is leukopenia at the height of the rash mainly caused by a drop in the lymphocytes.

The list of possible complications is long but fortunately the overwhelming majority of the patients recover uneventfully

Dermadromes.—Pale scarlatiniform or macular *premonitory rashes* are rare and very fleeting[141,142,143] and may disappear before the outbreak of the measles rash

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[140] Glanzmann, E Das kritische Dreitagefieberexanthem beim der kleinen Kinder (Exanthema subitum) Ergebn. d. inn. Med. u. Kinderh. 29 68-90 1926

[141] Rosecek, A. Masernbeobachtungen, prodromales Exanthem, Med Klin 23 490 1927

[142] Wieland, E Ueber fieberhaften scarlatiniformen Rash bei Masern. Monatschr f Kinderh. 42: 482-495, 1929

[143] Nöthen, P J Vorexanthem bei Masern Jahrb. f Kinderh. 86 2 1 222, 1922.

The *exanthem*[illegible] (Von Pirquet in Von Groer[illegible]) starts with pale pink spots from 1 to 5 mm in diameter *Intense itching may accompany the eruption* The spots are seen clearly first on the scalp behind the ears and between the shoulder blades less distinctly around the mouth and nose and in front of the ears. The cheeks offer a certain resistance but are soon invaded also On the second day a dense exanthem appears on the back and although less pronounced on the chest abdomen and mesial aspects of the arms. On the third and fourth days the development is completed with the invasion of the legs The emphasis



Fig 40 — Measles (Courtesy Dr Max Fox)

is on the head trunk shoulders and anterior surfaces of the arms and thighs *On the fifth day the appearance of new lesions usually stops.* With the return to normal temperature the spots fade in the order of their appearance leaving a pigmentation which is sometimes quite pronounced on the forehead There is a superficial branny desquamation which usually starts on the face from two to five days after the appearance of the exanthem [illegible]

The first lesions are follicular spots or slightly palpable papules surrounded by an anemic halo They grow quickly in size and number and become confluent, but the original follicular papular character can still be recognized within the larger bright red spots of the developed exanthem There is a great variability

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[illegible] Von Groer F Measles Pfaundler and Schlossmann Diseases of Children vol III Philadelphia 1935 J B Lippincott Company pp 170-212

[illegible] Kolly F Akute Exantheme Handbuch der inneren Medizin ed 1 Berlin 1934 Julius Springer

[illegible] Neuland, A Über Hautschuppung nach Masern Jahrb f Kinderh 115 203-224 1927

in the exanthems with regard to size of lesions, density and tendency to remain discrete or become more confluent. At its height the eruption is blotchy and dusky red. Miliary vesicles are quite common on the follicular papules. Increased seborrheic activity makes the skin feel greasy. The tourniquet test is usually positive.

While the exanthems may vary, great similarities of the rash in siblings as well as in individual epidemics have been observed, indicating the power of constitutional and microbic factors.

The histopathology of the measles[illegible] exanthem is characterized by vacuolization in the epidermis and a perivascular, predominantly lymphocytic infiltrate in the papillary body. There are small necrotic areas which correspond to macroscopic pustules. The absence of a horny layer in the oral mucosa produces the early erosions of the Koplik spots. It is not for very long that anything has been known about the peculiar formation of giant cells with 50 to 100 nuclei which occur in the lymphatic tissue of the tonsils, the respiratory tract and the esophagus, and which have been seen in appendices removed during measles (Warthin and Finkelday after Ravina and Levy Lang[illegible]; Manigi and Minami after Rietschel[illegible]).

Among the *anomalies* of the exanthem must be named first its absence, morbilli sine exanthemate. Usually the Koplik spots, too, are absent in such cases,[illegible] of which a great number have been well corroborated by the presence of all other symptoms, by the incubation period and by contact cases.[illegible]

While miliaria is common, bullous measles are rare. Confluent large bullae may, though rarely, cover and denude large areas so that the clinical picture of pemphigus results.[illegible] Hemorrhagic measles is rare; this variety has been seen in combination with bullous measles.[illegible] Swelling of the upper lip of two to three days duration is in some epidemics so common that one author has spoken of a measles lip (Oxenius after Robert[illegible]).

Measles, especially the hemorrhagic form, is sometimes followed by gangrene of localized areas of the skin.[illegible] Related to these cases are the multiple ulcerations which are known as *ecthyma gangrenosum*[illegible] which are occasionally seen after other infections, too, usually affecting infants. Ecthyma gangrenosum starts on the buttocks with hemorrhagic necrotic nodules or larger foci of cellulitis and leads to deep punched-out ulcers. The mortality is high. The condition is probably caused by secondary infection, especially with pyogenic cocci and *Pseudomonas aeruginosa* (*Bacillus pyocyaneus*).

[illegible] Ravina A and Lévy Lang P: Histologic Diagnosis of Measles: Specificity of Giant Cells; Appendicitis Caused by Measles, Presse méd 45 [illegible]1-[illegible] 1937

[illegible] Krassmann E: Masernähnliches Exanthem bei drei Geschwistern, Monatschr f Kinderh [illegible] [illegible]10-[illegible]11 1914

[illegible] Koeppe H: Masernähnliches Exanthem, Arch f Kinderh [illegible] 190-[illegible] [illegible]

[illegible] Selbiger G: Pemphigoide bullöse Masern and Pemphigus bei Masern, Monatschr f Kinderh [illegible] [illegible]-[illegible] [illegible]

[illegible] Linehan J J: Hemorrhagic Measles, Brit M J [illegible] [illegible] 194[illegible]

[illegible] Robert P: Infectious Skin Diseases Other Than Tuberculosis and Leprosy; Review of Literature, Dermatologica [illegible] [illegible] 194[illegible]

[illegible] Thorp E: A Case of Gangrene Following Measles, Lancet [illegible] 754 19[illegible]1

[illegible] Winstead J A: Gangrene of the Foot Following Measles, J Pediat [illegible] [illegible]-[illegible], 193[illegible]

[illegible] Takahashi: Ekthyma gangraenosum im Verlauf von Masern, Arch f Dermat u Syph [illegible] [illegible]-[illegible], 1914

Measles may affect *pre-existing skin diseases* in various ways. Infantile eczema[345] and prurigo[345] are often aggravated during measles[345] either by internal causes or by scratching during the itching eruption and desquamation periods. Psoriasis seems to improve but returns during convalescence [344] Measles like other acute infectious diseases often weakens the cutaneous tuberculin reaction The predisposing influence to skin tuberculosis is recognized.[346] Disseminated exanthematic, apparently hematogenous cases of lupus vulgaris and tuber culosis cutis verrucosa are not very rare after measles in countries where skin tuberculosis is more prevalent than in the United States

German Measles (Rubella)

The term German measles resulted from the long-combined efforts of German clinicians of the nineteenth century to separate a mild measles-like contagious disease from typical measles. When the International Medical Congress in London in 1881 tried to clarify the situation it was natural to speak of English measles and of German measles. Since then the entity has become widely recognized but there are still some dissenting unitarians. To prevent confusion it should be emphasized that the latin term rubeola is used for this disease in the German literature while in the English American terminology rubeola designates true measles (Dorland) The term rubella seems to be used only in the English-speaking countries.

The cause of the disease is unknown Children of 3 to 10 years of age are usually affected but no age group is immune. Lasting immunity after the disease is the rule.

The disease is best characterized by the often used expression mild measles The prodromal symptoms of malaise fever coryza and sore throat, which are not always present are much less pronounced than in measles. Children with German measles frequently come to the office of the dermatologist or are sent home from school because of the rash while a child with true measles is usually too sick to be ambulatory

The incubation period of rubella is from two to three weeks The fever is moderate and there is no photophobia or conjunctivitis. Excessive perspiration during the first to second prodromal days is a peculiar symptom (Stolte after Rietschel[347]) The palate and uvula are reddened and a few red follicles often appear along the midline (Forchheimer's sign) but there are no Koplik spots and the catarrhal symptoms, if any are mild

General *lymphadenopathy* is such an outstanding feature of the disease that Glanzmann advanced the theory that rubella is a disease of the lymphatic system not primarily an exanthem and therefore *toto caelo*" different from measles

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[344] Berk C H Immunity Against Psoriasis in Patients Who Have Previously Had Measles, Nederl tijdschr Geneesk 79 4187-4189 1935

[345] Costantino, G Sul comportamento dell eczema del lattante durante il morbillo, Clin pediat 12 216-228 1930

[346] Volk, R Tuberkulose der Haut, Handb d H u G k 10 1 1931

[347] Rietschel, H Rubella, Monatschr f Kinderh 88 242-245 1941

and scarlet fever Almost all the peripheral lymphatic nodes are swollen and tender and the mastoid occipital and posterior cervical glands particularly of the left side are so enlarged that the swelling often is not only palpable but visible The lymphadenopathy starts before the exanthem and may outlast it by several weeks. This generalized lymphadenitis may be the only sign of rubella In such exanthemless cases the diagnosis must depend on the accompanying circumstances, for example, contact cases with exanthem.[470]



Fig 41.—German measles. Quit copious rash (Courtesy Dr Max Fox.)

The blood shows an initial leukopenia and a later eosinophilia (8 per cent) In the course of the disease the leukocytes rise and the increase of the plasma cells becomes marked reaching 12 per cent.[471-472]

The *prognosis* is very favorable. The *treatment* is symptomatic.

Dermadromes —The exanthem which appears on the second or third day follows in many ways the pattern of measles. It is usually seen first behind the ears and on the nose but within one day it involves the whole body occasionally large areas remain free Th fresh spots are rounder more clearly defined and more regular than those of true measles. The most common size is that of a split pea although the rash may consist of smaller or larger spots. The color is

[469] Rietschel, H Acut Infectious Exanthems, The Diseases of Children, B Pfaundler-Schlossmann-Peterman vol III Philadelphia, 1935, J B Lippincott Company pp 213-233
[470] Rietschel, H Masern und Röteln, Monatschr f. Kinderh 71 84-90 1937
[471] Fibystrup O Rubella Without Rash, Brit J Child Dis 30: 20-23 1933
[472] Morawetz G Röteln R brotn, Handb d H 3 1 437-439 1930
[473] Feuerbach Röteln, Therap d Gegenw 83 76-77 1932

red a shade less bright than in true measles and fades quickly Often a confluent erythema develops on the face. The skin between the spots may especially on the back be diffusely red with the progress of the disease. Some epidemics have a pronounced hemorrhagic component.[illegible] The rash appears in successive crops, each of which lasts about twenty four hours. The whole exanthem lasts about three days. It fades in the order of the eruption [illegible] occasionally with a light dusty desquamation and faint pigmentation [illegible] The face and neck may be cleared while the legs are still red



Fig 43 —German measles Post auricular lymphatic nodes (Courtesy Dr Max Fox.)

The pharynx is diffusely red and the tongue often resembles the raspberry tongue of scarlet fever that is it is diffusely red not coated and the fungiform papillae are swollen

Roseola Infantum (Exanthema Subitum)

John Zahorsky[illegible] of St. Louis (in 1910 to 1913) separated from various little-understood exanthematic diseases of childhood a typical entity to which he unfortunately gave the old name of roseola infantum. The term erythema

[illegible] Zahorsky J Roseola Infantum Survey of Literature Arch Pediat 57 405-409 1940.
[illegible] Zahorsky J Roseola Infantum in J Brennemann Practice of Pediatrics, vol II Hagerstown, Md., 1937 W F Prior Company Inc

subitum[375] has become more popular while Glanzmann's[341] unwieldy name "critical three days fever exanthem of the infant" is used only rarely

The disease is an acute infection which at least in some countries attacks a large percentage of the infants. Rosenbusch[376] estimates that about 50 per cent of the young children become infected mostly at the end of the first year of life, rarely after the third year

The etiology is unknown but influenza has been suspected[377] The incubation period is seven days (from five to fifteen days, Sobel[44]) Lasting immunity results from the infection but a few cases of repeated attacks have been observed.[378,379] About 40 per cent of the cases occur in summer and only 18 per cent in winter[376]

The clinical picture is characterized by three days of continuous high fever and the eruption of a morbilliform rash immediately after the critical end of the fever The onset is sudden sometimes alarming with convulsions[380] headache and vomiting Sometimes however the children do not complain in spite of the fever Complications are almost unknown and in many cases the general well being is not disturbed Coryza and other mucosal symptoms and adenopathy are mild There is a characteristic drop of the polymorphonuclear leukocytes (2 to 20 per cent) and a relative lymphocytosis and mononucleosis (80 to 98 per cent)[380] These findings are most marked on the third day[75] The spleen is not enlarged The prognosis is invariably favorable in spite of the sometimes alarming onset.

Dermadromes —The *rash* appears as Glanzmann[344] poetically puts it as the aurora of recovery after the fever period. It starts on the back and covers the trunk within twelve hours sometimes leaving the face the scalp and the extremities free A second crop may then cover the limbs and remain visible when the first eruption has faded The rash consists of slightly raised rose spots from 2 to 5 mm. in size confluent or in irregular groups between which are small areas of normal skin Later a large confluent erythema may appear on the back suggesting scarlet fever There is no pruritus and the rash disappears in two or three days without pigmentation or desquamation There is no characteristic enanthem an important differential feature

The *diagnosis* may be difficult, especially in isolated cases. The most important feature is the eruption at, or after th fall of the temperature on the fourth day In measles the rash appears at the height of the disease the whole syndrome is more severe and infections among siblings are common In scarlet fever there is sore throat a typical tongue the exanthem appears early and

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[375] Veeder B. S and Hempelmann, T C Exanthem Subitum J A M A 77 1787-1790, 1921
[376] Rosenbusch H Exanthema subitum Schweiz med Wchnschr 60 1173-75 1930
[377] Opitz, H Masern, Exanthema subitum Kinderärztl Praxis 6-8, 1930
[378] Barenberg L H and Greenspan, L Exanthema Subitum, Am J Dis Child 58 983-993 1939
[379] Breese B B J Roseola infantum New York State J Med 41 1854-1859 1941
[380] Greenthal R M Roseola infantum, Wisconsin M J 40: 25-27 1941

lasts much longer and there is desquamation and leukocytosis. Rubella which may look very much like roseola infantum has the characteristic lymphadenopathy Erythema infectiosum rarely causes fever and the exanthem starts on the face especially over the bridge of the nose Drug eruptions and toxic and infectious erythemas must be considered No specific therapy is known

Erythema Infectiosum

Erythema infectiosum which is also known under a number of other names, for example fifth disease and megalerythema is a moderately contagious infection of unknown cause usually affecting children The disease occurs in epidemics of relatively small size often in institutions. The outbreaks are usually in late winter and spring Animal inoculation and bacteriological studies have not been successful However children have been infected by injection of blood taken at the height of the rash and by pharyngeal mucus.[342]

The incubation period is about nine to fourteen days but it was only twenty four hours in the experimental infections. There are no or very slight prodromes. The disease starts suddenly with a *rash* which is the main and sometimes the only symptom The exanthem appears first on the face as small red spots which soon grow and coalesce forming an erythema which is most pronounced over the cheeks and which leaves the perioral and periocular areas pale The erythemas of th cheeks are often connected by a red isthmus over the base of the nose so that a butterfly figure results. The erythema is usually bright red[343] sometimes pink or cyanotic[342] the fairly well-defined edges are slightly palpable and raised and the surface is smooth and in severe cases hot to the touch The chin is seldom affected the forehead is more often affected The patient looks as if he has been slapped on both cheeks so definite is the erythema[342]

One to two days later the erythema usually appears on the outer surfaces of the upper arms and sometimes on the buttocks and extensor aspects of the thighs[342, 344] The lesions are slightly papular and have a tendency to grow peripherally and to fade in the center Thus ring-shaped garlandlike zigzag lattice[345] honeycomb and other patterns result. The hands and feet are not affected There is only slight fever no enanthem and little itching From the third to the twelfth day the eruption fades but relapses may occur up to several months later Atypical rashes affecting only the limbs are rare.[346,347] Desquamation is usually lacking In a small portion of the cases the face remains free.[348] There

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[342] Tacconi G Sulla quinta malattia. Nuova epidemia osservata a Milano, Pediatria Arch. di pat e clin pediat 8 77 126 1928 Zbl 81 920

[343] Chargin, L Sobel, N and Goldstein, H Erythema Infectiosum Arch Dermat & Syph 47 467-477 1943

[344] Tobler L Erythema Infectiosum Ergebn d inn Med Kinderh 14 70-95 1915

[345] Romeo Lozano A Erythema infectiosum Pediatria espan 23 307-320 1934 Zbl 81; 88

[346] Klinger P Erythema infectiosum, München med Wchnschr 1939 II 1281

[347] Lawton, A L and Smith, R E Erythema Infectiosum Epidemic Arch Int Med, 47 28-41 1931

[348] Rector J M Erythema Infectiosum—Clinical Observations, J Pediat 15 840-845, 1939.

is moderate lymphocytosis and eosinophilia of 6 to 11 per cent[346-348] (Zikowsky [349] 20 per cent) during convalescence and later mononucleosis. Lymphadenopathy is uncertain The children twice as many girls as boys[347] are but little disturbed Complications are hardly ever seen and fatalities have not occurred

Febris Herpetica Febris Ephemera, Febricula

Febris herpetica febris ephemera, and febricula comprise a group of fevers of unknown etiology characterized by a high temperature for about one day with the usual complaints of an acute febrile disease. In many of these short fevers *herpes labialis* appears usually with sinking temperature or one or several days after the bout.[350]

Rubeola Scarlatinosa, or Fourth Disease, Dukes Filatow Disease.

Rubeola scarlatinosa is also called fourth disease and Dukes-Filatow disease There is much objection[348] to the acknowledgment as an entity of a febrile exanthem of which a few small epidemics have been observed

After an incubation period of from nine to twenty days that is much longer than in scarlet fever the disease starts with a pink, scarlatiniform slightly papular exanthem which covers the body within a few hours and does not always leave the circumoral area free. The face is generally less involved than the other parts The rash fades after one to three days and is followed by a slight branny desquamation The pharynx is red and the tongue only slightly coated.

The fever is mild and does not last longer than the rash There are no important complications.[348] There is no cross-immunity with scarlet fever the mild cases of which the disease resembles.

Miliary Fever (Sweating Sickness)

About 200 epidemics of miliary fever or sweating sickness have been described since the first outbreak frightened London in 1486 [351] No sporadic or endemic cases have been observed The epidemics usually occurred in spring or summer in an explosive form commonly restricted to relatively small areas like cities or valleys. The mortality of the epidemics varied from 0 to 90 per cent with an average of 8 per cent in the nineteenth century This is a greater fluctuation than is known of any other epidemic disease. The horror caused by the high mortality of some of these epidemics was augmented by the sudden outbreak and the fulminating course Frequently persons who had been in good health died within one or two days. More recently epidemics have occurred

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[348] Naegeli, O Blutkrankheiten und Blutdiagnostik, ed 5 Berlin 1931, Julius Springer
[349] Zikowsky J Erythema infectiosum Wien klin Wchnschr 1933, II 843-847
[350] Hirsch, O Febris herpetica Vienna, 909 Alfred Hölder
[351] Hirsch, A Der Friesel, vom historisch- und geographisch-pathologischen Standpunkt Virchow Arch f path Anat 8 484-533 1855 9 156-171, 1856.

in France[22] and Southern Germany and perhaps in Rumania.[22] The last certain outbreak was observed in some French hamlets by L. Rousseau[22] in 1926 with hardly any variations from the classic picture. No epidemics have become known in America.[22] The cause of the infection is unknown. The incubation period[22, 24] seldom exceeds one to two days but was found to be from ten to fifteen days in the cases of Stroé and Stroé.[22] Prodromes are either entirely lacking or consist of sudden weakness malaise and muscular pains. The onset is abrupt occurring frequently at night. A patient going to bed apparently in good health may awake with a chill bathed in sweat and feeling deadly sick. Precordial oppression a gripping dyspnea nausea and muscular cramps together with premonitions of death constitute acute attacks which follow each other rather frequently and in increasing strength. At the height of such a paroxysm death may occur.

The spleen is enlarged. The urine secretion is small even to the degree of complete anuria. Delirium is common. The fever is usually high and remittent in type.

The convalescence is slow and relapses may occur. Immunity is not certain. Mild cases occur but adults are more severely affected than children. The pathological findings are unrevealing. The content of the vesicles is not sweat but a serous exudate. No specific therapy is known.

Dermadromes.—The outstanding symptom after which the disease has been named is the excessive *sweating* (Timmermann[24]) which in contrast to sweats in other fevers starts with the rising temperature and continues throughout the duration of the fever. The sweating is so profuse that it is impossible to keep the patient even fairly dry by the most frequent changes of linen. The sweat is supposed to have a musty odor. After three to four days the characteristic rash appears. However many patients die before reaching the exanthematic second stage of the infection. The rash usually starts as a slightly papular eruption *on the neck and chest and spreads in several crops over the whole body*. The forehead and scalp are heavily affected and the face the least.[22]

The individual lesion is a red papule or macule with a central acuminate *vesicle which is at first yellowish and clear but after one to two days is opaque*. The exanthem may at times, especially in children be quite morbilliform but *confluent scarlatiniform* and hemorrhagic varieties have been seen in some epidemics.[22] The vesicles dry and crust after two to three days and heal with a branny or flaky desquamation. Oral lesions look like aphthae. The eruption is preceded by formication or tingling and accompanied by a feeling of relief

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[22] Rousseau L. La suette miliaire dans le Mont morillonnais Bull Acad d méd Paris 113 293-302, 1935

[23] Stroé A and Stroé H. Die Kinderschweissfrieselkrankheit Arch f Kinderh 96 78-80 1931

[24] Timmermann, H. Der Schweissfriesel Vienna, 1898, Alfred Hölder

Onyalai

Among the natives of West Central Africa occurs an acute febrile disease called onyalai the main feature of which is a mucocutaneous eruption of hemorrhagic bullae. These lesions are usually found inside the cheek on the tongue and on the palate although bleeding may occur from all mucous membranes. There may also be localized hemorrhagic lesions of the skin These blood blisters are umbilicated trabeculated and filled with loosely coagulated blood The disease may show all the features of a severe thrombocytopenic purpura.

Severe anemia icterus bronchopneumonia and central nervous system involvement are frequent. The mortality is high. There is profound thrombocytopenia with prolonged bleeding time normal coagulation time imperfect clot retraction and a positive tourniquet test The intramuscular injection of whole blood is said to be a good method of treatment.[illegible]

Glandular Fever (Infectious Mononucleosis)

Glandular fever (E. Pfeiffer[illegible]) or infectious mononucleosis is a contagious febrile disease of unknown etiology characterized by generalized lymphadenopathy splenomegaly and lymphocytosis. The incubation period is usually seven days. The terms glandular fever or prolonged fever[illegible] of pharyngeal-anginose thoracic abdominal nervous septic, and other types characterize the great variability of the disease. The prognosis is good [illegible]

Dermadromes.—E. Pfeiffer[illegible] emphasized the absence of exanthems, and Glanzmann [illegible] in his monograph on lymphemoid glandular fever elaborates on the lack of a characteristic rash Other authors,[illegible] however have occasionally or frequently[illegible] seen erythema multiforme and lichenoid morbilliform diffuse erythematous maculopapular rose spot-like or very rarely purpuric exanthema. The rashes appeared during the first two weeks.

The epidemic in London in 1930 was marked by unusually frequent typhoid-like rose spots which appeared before the lymphadenopathy Recently a rash incidence of 14 per cent has been reported (Minkenhof after Robert[illegible]) The blood count remains indispensable for the diagnosis. Of importance is the velvety red appearance of the gums which bleed easily In severe cases the teeth may submerge in these fragile tissues. On other parts of the oral mucosa especially on the soft palate small grouped papules may appear and cause a granulated appearance On such infiltrations shallow small or larger punched-out aphthous ulcerations may develop. Slight follicular and severe diphtheroid and

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[illegible] Mackie W K Onyalai Roy Soc Trop Med & Hyg [illegible] 1917
[illegible] Pfeiffer E Das Drüsenfieber Versammlung deutscher Naturforscher und Ärzte Köln, 1889
[illegible] Tid[illegible] H L Glandular Fever and Infectious Mononucleosis, Lancet 1934 II [illegible]
[illegible] Glanzmann E Das lymphämoide Drüsenfieber New York, 1930, S Karger
[illegible] Lehndorff H and Schwarz E Das Drüsenfieber Ergebn d. inn. Med u Kinderh [illegible] 1932
[illegible] J F J The Skin Eruption and False-Positive Wassermann in Infectious Mononucleosis (Glandular Fever J [illegible] Clin [illegible] 1941

ulcerative tonsillitis have often been reported. The oral ulcerations appear after the swelling of the submaxillary lymph nodes

Unilateral *conjunctivitis* of a dry granular character is not rare.[439] In exanthematic cases the Wassermann and Kahn reactions may temporarily become positive.[440]

Foot and Mouth Disease (Aphthous Fever)

Although the foot and mouth disease (aphthous fever) is predominantly an epidemic infection of cattle and other cloven hoofed animals it is occasionally transferred to man by contact with infected animals or drinking of their milk. The cause is a filtrable virus.

In man the infection has an incubation period of two days. The onset is sudden with fever headache and malaise On the following day salivation and an *eruption* of many umbilicated vesicles on the buccal and labial mucosa appear the lesions being surrounded by a bright red areola. The tongue and the pharynx may be similarly involved. On the third or fourth day the disease enters a second stage[441] New grayish or yellowish vesicles and larger blisters with or without red areolae may cover the hands and feet and even the legs.[442] The nail beds are often mentioned as the site of troublesome inflammations The nails may be shed or they may show transversal grooves. Maculopapular multiform and varicelliform exanthems involving the entire skin or much of it have been described[443-444] The mouth condition together with diarrhea rhinitis and conjunctivitis and the symptoms of general infection may cause an alarming picture Around the fifth day the symptoms subside and after ten days or more the patient is usually cured[445] The prognosis is good although some deaths have been reported The treatment is symptomatic.

The identity of human and animal infection has been corroborated by successful inoculation of human material into cattle[446] and guinea pigs.[447-448]

Dengue Fever

Dengue fever is an acute nonfatal widely distributed febrile disease of the warm climates It is transmitted by various mosquitoes including *Aedes aegypti* the carrier of yellow fever The cause is a filtrable virus.[449] The incubation period is about seven days.[450]

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[440] Von Schelts, L Maul- und Klauenseuche beim Menschen, Klin Wchnschr 1 630-632, 1931

[441] Vriese, L 2 Fälle von Maul- und Klauenseuche beim Menschen Berl tierärztl Wchnschr 37 231 1931

[442] Gibbon, A H *A Case of Foot-and-Mouth Disease* Lancet 1934 I 438

[443] Tappeiner S Maul- und Klauenseuche beim Menschen, Arch f Dermat u Syph 180 190-201 1940

[444] Gerlach Maul- und Klauenseuche beim Menschen und Uebertragung auf Meerschweinchen, Wien klin Wchnschr 37 310 1924

[445] Bertarelli Uebertragung der Maul- und Klauenseuche auf den Menschen und Wiederimpfung der menschlichen Krankheit auf die Rinder Zbl f Bakteriol. 43 625, 1907

[446] Waldmann, O and Pape J Experimentelle Untersuchungen über Maul- und Klauenseuche Berl tierärztl Wchnschr 37 349-354 1921

[447] Uhlenhuth, P Uebertragung der Maul- und Klauenseuche auf Meerschweinchen Deutsche med Wchnschr 47 671-672 1921

[448] Simmons, T S Dengue M Clin North America 27 808-821 1943

[449] Kisner P and Lisansky E T Dengue Ann Int Med 20 41-51 1944

The disease starts with severe frontal headache and pain in the lower back in joints and in muscles. Chills are marked and indolent lymphatic nodes are palpable over the posterior scalenus muscles.[411] There is bradycardia in spite of the high fever and leukopenia with a shift to the left. The temperature falls to normal on the third day but fever often returns after one to two days (saddle-back curve). The second fever is sometimes higher and ends by crisis around the seventh day. Deaths are very rare but convalescence may drag out over several weeks. No specific laboratory test nor treatment has been developed.

Dermadromes.—The initial fever is often (38 per cent Simmons[408]) accompanied by an erythematous symmetric rash or extensive flushing which is most pronounced on the face neck chest forearms and palms.[411] The eyes are reddened also. This flushing is out of proportion to the temperature and was seen in about 26 per cent of the cases during a recent major epidemic.[414] The flushing subsides gradually. If there was any erythema of the chest it may be converted into the secondary rash which does not involve the face. This secondary or terminal exanthem was seen more often (37 per cent Kisner and Lisansky[illegible] 86 per cent, Simmons[408]) It appears between the second and sixth days and is macular occasionally maculopapular scarlatiniform or rarely hemorrhagic. It usually starts on the chest, back or abdomen and spreads to the trunk but this sequence may be reversed if the rash starts later in the illness. No definite relationship seems to exist between the onset of the second fever attack and the terminal rash which is followed by an imperfect desquamation and itching of the palms and soles.[413]

Some authors emphasize the sweating and the variability of the rashes.[413] Complicating pyodermatoses are common.[illegible]

Pretibial fever. An epidemic febrile illness of approximately five days duration characterized by slight respiratory symptoms headache leukopenia palpable spleen and a symmetrical maculopapular rash mainly over both pretibial areas, vaguely resembling erythema nodosum has been observed among troops in South Carolina.[illegible] The rash was present in 80 per cent of the forty cases. All efforts to determine the nature of this pretibial fever were in vain.

Phlebotomus Fever

Phlebotomus, pappataci or sandfly fever is a benign sandfly-borne virus infection of hot and dry countries, characterized by a fever of two to four days duration severe frontal headache and eye-ache photophobia and muscular pains. There is leukopenia and shift to the left. The face is described as curi

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[411] Stewart, F. H. Dengue. U. S. N. M. Bull. 42: 1333-1476, 1944.

[412] Aalsmeer, L. Yellow Fever and Dengue. J. Pediat. 22: 613-617, 1943.

[413] Mlinaric, H. Beobachtungen bei einer Epidemie von Dengue Fieber mit mannigfaltigen Symptomen. Acta dermat. 20: 61-66, 1933. Zbl. 43: 231.

[414] Dracoulides, N. Observations dermatologiques au cours de la dengue (pendant la pandémie d'Athènes, en 1928). Bull. Soc. franç. de dermat. et syph. 36: 613-618, 1929.

[415] Daniels, W. B. and Grennan, H. A. Pretibial Fever an Obscure Disease. J. A. M. A. 122: 361, 1943.

ously red and puffy in contrast to the body[416-417] and may stay so for weeks after the fever The conjunctivae are red and there is photophobia. Crops of vesicles at the junction of the hard and soft palates[418] (not seen by other observers) and probably only in a minority of the cases purpuric scarlatiniform morbilliform urticarial and erythema multiforme-like evanescent rashes[417] and perifollicular erythema in the axillae and about the elbows and knees have been mentioned. Herpes is not a feature[416-418] but occurs occasionally[417] in severe and atypical fashion

Bullous reactions and severe edema following sandfly bites after convalescence are interpreted as allergic reactions.[417]

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416 Walker A S and Dods L Epidemic of Sandfly Fever in Palestine During 1940 M J Australia 28: 345-349 1941.

417 Marchionini A Haut und Schleimhauterscheinungen beim Pappatacifieber in Anatolien Arch f. Dermat u. Syph 182: 612-651 1942.

418 Schilling, C Pappatacifieber Handbuch der inneren Medizin, vol I Berlin 1925, Julius Springer

419 Sabin A. B Philip, C B and Paul, J R Phlebotomus (Pappataci or Sandfly) Fever J A.M.A 125 693-700 1944

CHAPTER V

SYSTEMIC INFECTIONS

Varicella (Chicken Pox)

In 1931 Tezner [illegible] in a comprehensive review of the subject stated that the causative agent of varicella (chicken pox) has often been searched for and almost as often found This is a witty overstatement. We know that it is a dermatropic, probably filtrable virus related to but not identical with Paschen s elementary bodies which cause variola and vaccinia. Injection of the content of the vesicular lesions of chicken pox into the rabbit s cornea produces within twenty four hours a small vesicle which bursts after seventy two hours. The microscopic picture of the cornea is quite characteristic especially the giant cells with large eosinophile inclusions found by Gins (see Tezner[illegible]) Tyzzer (after Lipschütz[illegible]) found nuclear inclusions which Lipschütz[illegible] believed to be microscopically identical with the inclusions found in herpes zoster (zoster bodies)

The virus is contained in the skin lesions and probably in the blood stream Experimental skin infection with nasal mucus has been as unsuccessful as the infection of the tonsils with vesicular fluid but the intradermal inoculation of blister serum produces after nine days a typical vesicle which always remains localized and can be successfully used for further inoculations. The inoculation is unsuccessful in persons who have had varicella. It immunizes against chicken pox with considerable reliability [illegible]

Droplet infection through the lungs seems to be the most important way of contagion indirect transfer is negligible.

Chicken pox is endemic and epidemic usually affecting children Varicella has a good prognosis unless one of the rare complications occurs. Newborn infants and adults are much less frequently but usually more severely affected [illegible] The infection is followed by long lasting immunity

The incubation period varies from seven to twenty-six days but is usually thirteen to fourteen days. Prodromes are little marked Fever is common especially in older children or adults and convulsions sleepiness photophobia and gastrointestinal symptoms may occur Very short lived prodromal or initial rashes are not common (1 per cent) They are mostly scarlatiniform rarely

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[illegible] Tezner O Varicellen. Ergebn d inn Med Kinderh 41: 843-852, 1931

[illegible] Lipschütz, B Die Epitheliosenkrankheiten der Haut, Handb d H Gk 2: 81 104 1932.

[illegible] Lipschütz B and Kundratitz, K Ueber die Aetiologie des Zoster und über seine Beziehungen zu Varicellen, Wien klin Wchnschr 38 499-503 1925

[illegible] Greenthal, R M Prophylaxis of Varicella With Vesicle Fluid, Am J Dis Child 31 851-855, 1926

[illegible] Waring, J J Neubuerger K and Geever E F Chickenpox, Severe Forms in Adults, Arch. I Med 69 384-409 1942

[illegible] Nebe Karl Ueber Varicella bei Erwachsenen, Leipzig, 1931 Dissertation

morbilliform or polymorphic and seem to forecast a more severe course. Giant cell formation in the tonsils similar to that seen in measles has been found in chicken pox during the prodromal stage.[69] All symptoms may be absent and the exanthem may break out with the patient in apparently good health. This conspicuous lack of sick feeling often causes the child with varicella to be brought to the office of the dermatologist because the idea of a systemic infection does not enter the mother's mind. This rarely happens in the other important exanthematic diseases of children.



Fig. 43.—Varicella. (Courtesy Dr. M. Fox.)

Dermadromes.—The eruption starts on the face and on the scalp, that on the body (back) being only slightly later, though some isolated vesicles may precede the main eruption. The distribution of the exanthem, which may develop fully in one to two days, is most dense on the trunk and becomes lighter toward the extremities and the acra. This centripetal tendency is in marked contrast to the centrifugal distribution of the variola pustules, which leave the trunk and especially the abdomen relatively free and crowd on the hands and feet. The individual lesion appears as a small macule which in twenty-four hours develops into a clear vesicle which is often surrounded by a relatively wide bright red areola. The blister is sometimes oblong, rarely pustular or hemorrhagic. Pri-

[69] Tomlinson, T. H.: Chickenpox Giant Cell Form in Prodromal Stage, Am. J. Path. 15: 523-526, 1939.

mary umbilication of the filled lesions is rare though early rupture, depression and formation of a sunken crust in the center may suggest umbilication but should not be taken as such The vesicle is multilocular, but the septa as well *as the wall are much thinner than in small pox* so that the lesion often can be "wiped off" with a rough towel The blister is quickly followed by a crust which



Fig 44 —Bullous and hemorrhagic chickenpox (Courtesy of Division of Dermatology Department of Medicine University of Chicago)

may adhere for many days or as long as two weeks A few larger and deeper lesions may leave pitted scars with pigmented margins but the marks are rarely disfiguring The lesions are more numerous on irritated or macerated skin The exanthema vary in density from a few lesions to a copious eruption of many hundreds of efflorescences, in all stages of development. This latter peculiarity is due to the appearance of successive crops and to the fact that the individual lesion may become arrested in any stage of development. The crops may be

accompanied by mild fever After one week the crops stop appearing although miliaria like weak eruptions may continue to follow The last eruptions are mild and the lesions usually fail to mature to vesicles

There are several *clinical varieties* of chicken pox and its complications.[44-47] The eruption may form bullous impetiginous or coalescent lesions. Confluence indicates a severe infection



Fig 45 —Varicella gangrenosa Fatal case. (Courtesy Dr Max Fox)

Varicella pemphigoides is a rare variety characterized by large flaccid bullae with adherent centers. Such cases may be accompanied by high spiking temperatures[[illegible]] and have repeatedly taken a fatal course[48] Some of these cases seem to be a combination of varicella and secondary pyogenic infection Erysipelas is a dangerous complication In some cases the vesicles remain very small this is called *miliaria varicellosa*

In *varicella gangrenosa* the normally fast sequence of drying and crusting of the vesicles is disturbed by a progressive necrosis which leads to punched-out gangrenous ulcers The floor of these ulcers is covered with necrotic greenish material Hemorrhagic features are common so that the ulcers often appear black. However an occasional black discoloration of the otherwise normal crusts does not warrant the diagnosis of gangrenous chicken pox Several ulcers may coalesce so that palm-sized gangrenous defects ensue which may even lay bare the underlying muscles In some instances the gangrene started in apparently normal skin and not from the vesicles

[47] Ronaldson G W and Kelleher W H Chickenpox, Anomalous Forms Brit J Child Dis 25 23-24, 1928

[48] Schwartzman J Varicella and Pemphigus Acu es Arch Pedia 57 [illegible] 1940

Gangrenous varicella is a severe disease with high temperature prostration and often fatal course Infants and sick youngsters are more likely to develop this complication than older and otherwise healthy children. Scarlet fever diphtheria, and tuberculosis are among the predisposing diseases. Banks and McCartney [illegible] in a fulminating case of massive skin gangrene in the eruptive stage of varicella, found streptococci to be the causative organism. Hemolytic streptococci are also the cause of dangerous cellulitis and of erysipelas and lymphadenitis. Infected lymph nodes usually break down and form abscesses. Cutaneous complications amount to 57 per cent of all the complications of chicken pox.[illegible] The incidence of gangrenous varicella amounts to about 1 per cent,[illegible] but seems to be much smaller in the United States. More than one half of the reported cases of gangrenous varicella ended fatally



Fig 46 —Hemorrhagic and unusually copious varicella (Courtesy Dr Max Fox)

Knoepfelmacher[illegible] separates from other *purpuric* manifestations *in varicella* the prodromal purpura and the purpura which occurs not too infrequently in mixed infection of pertussis and varicella. The varicella eruption is rarely hemorrhagic from the start. The vesicle content may become bloody or there may be other purpuric features the whole syndrome of thrombocytopenic purpura[illegible] may develop during or after the infection in rare instances together

[illegible] Banks, H S and McCartney J E Varicella Gangrenosa Due to Streptococcus Pyogenes, Lancet 1937 II 311 314

[illegible] Bullowa, J G M and Wishik S M Complications of Varicella Their Occurrence Among 2,534 Patients, Am J Dis Child 49 923-926 927-932 1935

[illegible] Knoepfelmacher Varizellen und Hautblutungen Wien med Wchnschr 1916, p. 990

[illegible] Cohen, H J Acute Thrombocytopenic Purpura Following Varicella, Arch Pediat 53 773-776, 1936

with massive skin gangrene.[433] Pyogenic sepsis has been blamed in some of these cases.[437]

The diagnosis of chicken pox is only difficult in unusual types, in isolated cases, or in times of a smallpox epidemic. Many authors discuss the differential diagnosis of chicken pox and smallpox[438-439] (Tièche after Tezner[439]). The most important points are: In chicken pox as compared with smallpox, the prodromes, especially fever, are mild or lacking. The distribution of the rash is centripetal, starting and massed on the trunk. It appears in crops, and the lesions show different stages of maturity. The lesion is generally less round and less firm so that it can be wiped off and it is rarely umbilicated. The halo (corona) is more irregular, wider and it develops faster. These criteria should all be taken with a grain of salt and the diagnosis should not rest on any one sign or symptom. (See also under Variola.)

No specific laboratory test for chicken pox has come into general use, so that a negative Paul's test for smallpox may, in certain cases, become an important diagnostic aid.

Occasionally *Kaposi's varicelliform eruption*, a rare acute vesiculopustular eruption with severe systemic reactions, may have to be considered. In most of the known cases the rash was superimposed on atopic dermatitis. The umbilicated lesions resemble vaccinia more than varicella, but they appear in crops and the Paul test is negative. There is increasing evidence that the disease is a generalized herpes infection.[440-443]

Herpes Zoster and Varicella

As far back as 1891 Von Bokay[444] published reports of five different instances of chicken pox in children following herpes zoster in a parent or other contact after a period approximately equal to the incubation period of varicella. These observations, apparently easy to check, were almost ignored until in 1909 the same author[444] presented a second series. Since then far more than 300 cases have become known and the puzzling matter continues to appear in additional publications.[445,446] The most common type of relationship between the two diseases is an outbreak of varicella in one or several persons who have had con

[437] Steiner, A. V., and Lockwood, W. W.: Varicella Complicated With Thrombocytopenic Purpura and Gangrene. J. Pediat. 12: 641-647, 1938.

[438] Wesselhoft, C.: Differential Diagnosis of Chickenpox and Smallpox. New England J. Med. 230: 15-19, 1944.

[439] Laidlaw, F. W.: Smallpox and Chickenpox: Differential Diagnosis. New York State J. Med. 28: 210-212, 1928.

[440] Blattner, R. J., Heys, F. M., and Harrison, M. L. K.: Etiology of Kaposi's Varicelliform Eruption. J. Pediat. 27: 207-2[illegible], 1945.

[441] Lynch, F. O.: Kaposi's Varicelliform Eruption. Arch. Dermat. & Syph. 51: 129-137, 1945.

[442] Lane, C. W., and Herold, W. C.: Kaposi's Varicelliform Eruption. Arch. Dermat. & Syph. 50: 396-404, 1944.

[443] Evans, C. H., Botts, V. S., and Steves, R. J.: Kaposi's Varicelliform Eruption. Arch. Dermat. & Syph. 51: 124-125, 1945.

[444] Von Bókay, J.: Ueber den aetiologischen Zusammenhang der Varicellen mit gewissen Fällen von Herpes Zoster. Wien. klin. Wchnschr. 1909, p. 1323; Jahrb. f. Kinderh. 106: 8-23, 1924.

[445] Blatt, M. L., Zeldes, M., and Stein, A. F.: Chickenpox Following Contact With Herpes Zoster: 2 minor epidemics. J. Lab. & Clin. Med. 25: 9[illegible]1-955, 1940.

[446] Barker, L. P.: Generalized Herpes Zoster: 8 cases. Arch. Dermat. & Syph. 40: 874-896, 1939.

tact with a person suffering from herpes zoster In several instances accidental chicken pox infection from other sources could be fairly conclusively ruled out for example in Lynch's[443] case by the fact that the hospital where the case oc curred was in quarantine for twenty-one days because of scarlet fever while the incubation period of chicken pox rarely exceeds seventeen days. Occasionally



Fig 47 —Herpes zoster in varicella (Courtesy of Division of Dermatology Department of Medicine, University of Chicago.)

secondary cases of varicella developed from those varicella cases which stemmed from herpes zoster thus proving their true chicken pox nature However these infections did not prove as highly contagious as is usual [443, 444] The appearance of herpes zoster after contact with chicken pox is seven times rarer than chicken

[443] Lynch, F W Herpes Zoster and Chickenpox, Arch Dermat & Syph. 43 66-80 1941.
[444] Montinelli, M. Herpes Zoster e varicella Boll Soc ital pediat 3: 183-185, 1934.

pox after zoster [444] Very rare too are the sequences chicken pox—herpes zoster—chicken pox or zoster—zoster—chicken pox or other alternations Chicken pox, simultaneously with or following herpes zoster in the same person usually an elderly man varicella with herpetiform groups of vesicles, and herpes zoster with aberrant or generalized lesions have been reported [445] The cases in which

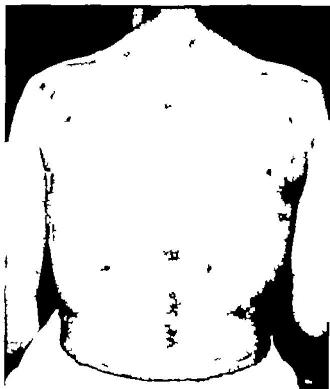


Fig 48 —Varicella in adult ith herpes zoster Same patient as in Fig. 47 (Courtesy of Division of Dermatology Department of Medicine, University of Chicago)

one disease followed the other have been interpreted in favor of a close relationship or identity of the diseases[446] as well as to prove their different nature since immunity which probably follows herpes zoster and certainly follows varicella would be more likely to prevent the sequence than to produce it [447] The interpretation of the relationship between herpes zoster and varicella as a fortuitous one is refuted by the apparent lack of any co-occurrence between for example herpes zoster and measles which should occur just as often if coincidence were the only factor The most interesting experimental study was made by K

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[445] Fleming, J Herpes and Varicella Simultaneously in Same Patient Glasgow M J 132: 72-73 1939

[446] Perriman, D G Chickenpox and Herpes Zoster in Same Patient, Lancet 1939 I 930-931

[447] Schönfeld, W Herpes Zoster und Herpes Simplex, Handb d H Gk 7 1 1 122, 1928

Kundratitz[448] who in seventeen out of twenty-eight cases successfully inoculated herpes zoster into children who had not had chicken pox. Two of the inoculated children developed after the varicella incubation period a generalized eruption identical with varicella The inoculation was never successful in children who had had chicken pox and those children who had been successfully inoculated with herpes zoster or who had been treated with zoster-convalescent serum proved to be immune to varicella. Lipschütz[illegible] found nuclear inclusion bodies



Fig 40.—Chickenpox and herpes zoster The chickenpox preceded the eruption by a few days (From Top, Franklin H Handbook of Communicable Diseases, The C V Mosby Company)

which he believed to be characteristic of both diseases, in the inoculation reactions of Kundratitz's[448] cases. Kundratitz's experiments were on the whole confirmed by Bruusgaard[449] Experimental infection with varicella stemming from herpes zoster just by placing the beds of the children close together was accomplished several times by Braslavsky[450] A new contribution is the finding of similar inflammatory changes in the spinal ganglia in varicella as are known to occur in

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[448] Kundratitz, K Experimentelle Uebertragungen von Herpes Zoster auf den Menschen und die Beziehungen von Herpes Zoster zu Varicellen, Monatschr f Kinderh 29 516-523, 1925.

[449] Bruusgaard, E The Mutual Relation Between Zoster and Varicella, Brit J Dermat 44 1-24, 1932

[450] Braslavskii, P Herpes Zoster and Varicella, Kiev med Z N 3 and 4 42-43, 1930 Zbl 36 351

herpes zoster [41] Some authors believe that the incidence curve of herpes zoster and varicella runs parallel

All theoretical explanations of the relationship between herpes zoster and varicella have so far remained unsatisfactory [41,42,43] mainly because of varicella zoster cases in the same person. Unitarian and dualistic schools of thought have formed ranging from complete denial of any relation to close relationship with dermatropism of the virus in varicella and neurotropism in zoster The matter is still highly controversial [43] however some relationship cannot be doubted

Vaccinia

Vaccinia is an infection of cattle caused by a virus which seems to be identi cal with that of variola Animal passage probably has modified the infection in many respects. It almost always causes a characteristic pustule at the site of infection followed only in extremely rare instances by generalized eruptions.

The disease leaves the patient immune to vaccinia and smallpox. Spon taneous infections with vaccinia are quite rare and occur mostly in dairy per sonnel. The intentionally produced infection with vaccinia however is one of the most common and widely studied infectious diseases of the civilized world Though produced in order to attain a systemic effect that is immunity against variola vaccinia is usually not thought of as a systemic infection

The first three to four days after inoculation is the symptomless incubation period On the fourth day a raised papule (papilla) with a narrow red halo (aula) appears. On the sixth or seventh day the papule changes into an umbili cated vesicle surrounded by a wide areola. Between the eighth and tenth days the infection is at its height and often accompanied by lymphadenopathy fever and leukocytosis. According to some authors the spleen is palpable for a short while The involution of the pustules starts on the eleventh day Three to four weeks after the vaccination the local process has wound up with a scar

The apparently solid papule appears histologically to be a vesicle with many chambers. There are characteristic vacuolizations of the cytoplasm characterized by Unna [44] as ballooning and reticular degenerations. The first term was chosen because of the vacuolization which finally leaves the prickle cells looking like bags filled with balls, the nuclei The epithelial and other cells of the vesicles contain the variola vaccinia virus. Inoculation of the vesicle content into the cornea of the rabbit (Paul s test) produces in thirty-six hours characteristic epithelial papules with central crateriform necrosis. The micro-scopic examination demonstrates many Guarnieri bodies.[44] Paschen s elementary bodies can be demonstrated in smears from early lesions by staining They resemble cocci but they are smaller

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[41] Balogh E V Zur Entstehungsweise der Windpockeneruptionen Ein Beitrag zur Frage Varicellen und Nervensystem Verh 9 in ernat Kong Dermat 2 232 241 1936

[42] Nohara F J Beobachtungen on Zoster gleichzeitig mit Varicellenausschlag bei demselben Kranken-Dermatologica 791 29-43, 1939

[43] Braun O K mer L Nagell O Rille J H and Schönfeld, W Beziehungen Zwischen Zoster und Varicellen Dermat Wchnschr 1935 I 208-214

[44] Paschen E Vaccine and Vaccineausschläge Handb d H Gk 2 161 207 1932

A great number of investigations have shown that the vaccinia virus enters the blood stream and appears in the air passages, in almost all the organs[illegible] and in the secretions *for example the urine.*[illegible]

The blood of vaccinated children without any complications may from the third to the tenth day produce typical vaccinia in nonvaccinated children (H and K. Herzberg after Paschen)[illegible]

Dermadromes —In spite of the generalization of the virus which probably occurs in all cases hematogenous skin infection and development of typical lesions are extremely rare. These lesions must be separated from accidentally inoculated vaccinia on eczematous skin on the lips, on the eyes or on other susceptible parts



Fig 40 —Vaccinal rash. (Courtesy Dr Max Fox.)

of the surface (eczema vaccinatum) True *generalized vaccinia* appears possibly after the third day but usually during the second week after the vaccination as a papular rash which passes through vesicular and pustular phases though not with the precision of the inoculated vaccinia The eruption is disseminated sometimes universal Exanthems are known Sometimes the neighborhood of the original vaccination for example the same arm is especially involved The content of the pustules produces characteristic lesions in the rabbit cornea and in the skin of nonvaccinated persons. The eruption is accompanied by moderate

[illegible]Gins, H A Hackenthal H and Kazanzewa, Natalie Neue Erfahrungen und Versuche über die Generalisierung des Vakzinevirus Centralbl f Bakteriol 110: 113-118, 1929 Experimentelle Untersuchungen über die Generalisierung des Vaccinevirus beim Menschen und Versuchstier Ztschr f Hyg u Infektionskr 110: 429-44 1929

[illegible]Wolfsohn Ueber Vaccine generalisata und Nachweis des Virus im Urin Ibid. 87 487-488.

fever and splenomegaly The differentiation from variola and varicella may be of practical consequence In contrast to smallpox there are no severe prodromes and no initial rash There is no drop in temperature following the eruption The acme is reached at the time of pustulation and is followed by slow lysis. The pustules have no areola, they are larger and they heal without scars (Drago after Paschen[454]) Severe varioliform cases with fatal outcome have been described[457,458,459] The microscopic picture in Shortt's[458] case was that of



Fig 8 —Hemorrhagic and extensively generalized vaccinia (Courtesy Dr Max F [illegible])

vaccinia Corresponding changes were found in focal lesions of the spleen and liver[460] A pemphigoid eruption of the fetus after vaccination of the mother may occur[461]

Morbilliform urticarial bullous or rarely erythema multiforme-like exanthems occasionally appear during the second week rarely earlier

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[457] Anders Allg Kuhpocken mit tödlich Ausgang Ztschr f Hyg u Infek Krankh 89 116, 1919

[458] Shortt, O T de Vere Case of Generalised Vaccinia Lancet 1933 I 580-581

[459] M Khann, O F and Ross R A Generalized Vaccinia and Eczema Vaccinat m M Clin North America 21 785, 1938

[460] Rous, R A Virus and Rickettsial Diseases, Cambridge Mass 1940 Harvard University Press.

[461] Lynch, F W Dermatologic Conditions of the Fetus With Particular Reference Variola and Vaccinia, Arch Dermat & Syph 26 997 1019 1932

These eruptions may be analogous to the initial rashes in variola The postvaccinal rashes have rarely been seen after revaccination.[482] The cause of postvaccinal rashes as well as of true generalized vaccinia is thought to be a disturbance of the antibody formation Normally these substances are produced in sufficient quantities to neutralize the virus in the blood stream so that no exanthem appears. In other cases enough of the blood borne virus reaches the skin to cause an erythema. In the papulovesicular generalized vaccinia the antibodies are so weak or they appear so late that the virus deposited in the skin can complete a fairly normal development (Czerny and Opitz after Groth[483-484])

Hemorrhagic vaccinia and purpura after vaccination are very rare[485-486-487] (Voigt after Paschen[485]) The pustules are black and they bleed there are signs and symptoms of thrombopenic purpura. The prognosis seems favorable.

Some authors claim that the number and quality of the scars of the first vaccination indicate the degree of immunity which has been reached (Gregory after Paschen[485]) [488] In spite of great numbers of observations in revaccinated children no consensus has been reached Armstrong[489] found that out of seventy one cases of postvaccination encephalitis in America seventy followed vaccination with one scratch only It is conceivable that too little skin reaction may not produce sufficient immunity to protect against such complications.

Psoriasis may either develop at the site of the pustules or increased psoriatic activity and spreading may follow While the localized eruption can be interpreted as a Koebner phenomenon (provocation of psoriasis by local irritation) the flare up and generalization of psoriasis is well known to occur after many infections

The relation of so-called *milkers nodules* on the hands of dairy personnel to true vaccinia is controversial.[490-491-492] Vaccination does not seem to immunize against milkers nodules (Nagel after Robert[344]) Rashes similar to postvaccinal eruptions have been observed[493] in milkers nodules.

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[482] Beretta, S Polymorphes Exanthem als Komplikation einer akzidentellen Vakzination, Dermat. Ztschr 60: 280-285, 1931

[483] Groth, A Vaccina generalisata, Zbl f d ges Hyg 10 865-867 1926

[484] Groth, A Zur Aetiologie der Melkerknoten, München. med. Wchnschr 76 2128-2130, 1929.

[485] Paschen E Fall von Purpura im Anschluss an die Impfung, München med Wchnschr 1907 p 1901

[486] Heaton, T G Purpura Associated With Vaccination, Canad M A J 43 593-594, 1940

[487] Schwartz, A B Postvaccinal Purpura Case, Am J Dis Child, 39: 584-586, 1930.

[488] Stadler H Die Impfnarben als Indikatoren der Immunität gegen Variola und Vakzine Veröffentl d Geb d Med Verwalt 42: 383-404 1934

[489] Armstrong, Charles Post vaccination Encephalitis, With Special Reference t Prevention, Pub Health Rep, 47 1553-1568 1932

[490] Oppenheim, M and Fessler A Ueber Melkerknoten, Arch. f Derm Syph 159 334-342 1930

[491] Schultze W and Grandberr F J Ueber Melkerknoten mit toxischem Exanthem, Arch f Dermat Syph 158: 1 18 1929

[492] Tolstov A and Mordsov M Histology of Milker' Nodes, Sovet vestnik venereol i dermat. 9 339-343, 1931 Zbl 39 368

[493] Stark, A M and others Ueber die Pockenätiologie der sog Melkerknoten. Arch f. Dermat Syph 170 30-40 1934

[494] Wortmann F Deux nouveaux cas de tubercules du trayeur Bull Soc franç de dermat. et syph. 41 197 202 1934

[495] Pommer, B J Ueber Melkerknoten, Dermat Wchnschr 98 134-142, 1934

[496] Kren, O Melkerknoten mit Exanthem, Wien. klin. Wchnschr 21 1301, 1930

Variola (Smallpox)

Smallpox is an extremely contagious usually epidemic, disease. It is caused by a virus in many points identical with that of vaccinia.[64-67] As in vaccinia the agent is contained in the cellular inclusions found in the lesions (see vaccinia). The characteristic inclusions, Guarnieri's bodies can be demonstrated in the small grayish ulcerated papule which develops after inoculation into the rabbit's cornea (Paul's test). The disease is probably contagious even in the initial stages. *The virus is spread by* contact, droplets dust or contaminated persons and objects. The crusts of the healing lesions are highly contagious as are the bodies of persons who have died from the disease. Air and sunshine destroys the germs which otherwise are able to survive for a long time. The disease confers immunity although occasional reinfections have been reported. Almost all persons who neither have had smallpox nor have been vaccinated during the preceding ten years are susceptible. The fetus may become infected and be born with an exanthem or with scars.

The *incubation* period is twelve days with some variations and it is a rule that the shorter the incubation the severer the course. Thus, in hemorrhagic smallpox the incubation period is often only eight days while in the mild variola minor the incubation period may be twenty-one days.[64] The *onset* of the disease is abrupt. The patient is severely ill with high temperature frontal headache and intense lumbar and other muscular pain. Vomiting and constipation may be present. Delirium is common. The skin is flushed and hot. Women often start to menstruate at the outbreak of variola sometimes before the expected day. Most authors agree that *severe prodromes do not necessarily usher in a* severe eruption although a mild initial stage is usually followed by a mild course.

Dermadromes.—A peculiarity of the prodromal phase of variola is the *initial rash* which is observed in 15-30 per cent of the cases. It most often develops on the second day and is morbilliform or scarlatiniform rarely urticarial. The morbilliform rash starts on the face and travels within a few hours, over the body and especially over the extremities. It is most often recognizable on the sides of the body on the extensor surfaces of the extremities and on the mammae. It vanishes as quickly as it appears. Some authors[75] believe that the purely macular non petechial rash is of favorable prognostic significance but this is not always true.[75] More importance is given to the much rarer scarlatiniform rash. In this variety which may be seen on the very first day of the prodromes, the abdomen below the navel and the inner thighs are flaming red. Within this somewhat triangular shaped area (Simon's thigh triangle) petechiae can frequently be demonstrated.

In some instances similar erythemas may appear on the shoulders and on the inner aspects of the upper arms. They may be more dense on the vaccinated arm if not too much time has elapsed since the successful vaccination.[67] This *erythema variolosum* vanishes relatively slowly. It may still be seen in the early

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[65] Haagen, E. Aetiologie der Pocken. Arb. Reichsgesundhamt 69 149-163, 1938
[66] Tomaselli M. and Iacono B. The Initial Exanthem of Smallpox J. Infect. Dis. 29 109-113 1921
[67] Morawetz, G. Variola, Handb d H Gk 14 1 443, 483 1930

eruption period and it has often been said that the sites of the initial erythema either remain free of pocks or have relatively few. The petechiae seen in the initial rash should not be confused with the rare purpura variolosa.

The end of the third day marks the end of the initial stage and the beginning of the decisive *eruptive period*.

The *variola exanthem* appears first on the face and head. Within three days it invades the trunk and then the extremities. The face is usually the most densely covered part. Areas subject to friction as the garter and belt areas or skin which has been irritated by iodine or other irritants or the macerated folds of the groin may produce a richer crop of lesions. Face, extremities and trunk, in the order named, show decreasing degrees of density. The abdomen is the

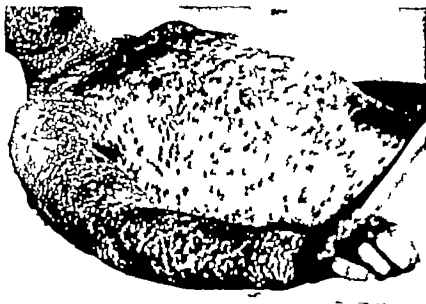


Fig 32.—Smallpox, sixth day. Severe case with confluent rash in the face. (Courtesy Dr Ma Fee.)

least affected region. However, all these degrees are relative and vary widely with the severity of the case.

The individual lesion, which is accompanied by a slight burning or itching, begins as a pinhead sized papule which grows to a bright red lentil or split-pea sized efflorescence within one to two days. On the third day of its existence the papule develops a small vesicle on its center which within two or more days extends over the whole lesion. Its content changes on the fifth day from the initial clear serum to an opalescent fluid and finally to frank pus on the sixth day (ninth day of the disease). This marks the beginning of the pustular stage. The content of the vesicle is under considerable pressure, often giving the palpating finger a firm shotty sensation. This feature, however, has been overemphasized and it may be entirely absent. It is not possible to relieve the pressure by needle

puncture since the vesicle is multilocular The center of many lesions becomes *navel like while the edge appears raised* The pustules are surrounded by a bright red narrow halo The skin between the pustules is often swollen

The outbreak of the variola exanthem is accompanied by a sudden drop in temperature after which the patient feels greatly relieved In mild cases the temperature continues to fall throughout the eruption while in the more severe *cases the temperature rises again with or even before the pustulation* The maturation of the pustules takes place in the order of their appearance so that the face is always one step ahead The duration and the severity of the pustular stage varies. While in some cases the small number and the short lifetime of the pustules may affect the general condition but little a copious or confluent



Fig 83 —Confluent smallpox (Courtesy Dr Watson Campbell and Dr O S Newman, from Sutton and Sutton Diseases of the Skin, The C V Mosby Company)

exanthem causes great suffering with recurrence of high temperature and delirium and all the possible complications of a highly toxic and septicemic state Skin gangrene not related to bed sores has occasionally been observed Most of the deaths occur in the suppurative stage While the widespread inflammation of the skin naturally makes the patient most uncomfortable much of his suffering comes from the *mucosal* eruptions. The mucosal efflorescences follow the same pattern as the skin lesions papules, vesicles pustules. However the roof of the vesicles is destroyed early so that instead of the pustule an erosion develops. The mouth the nasopharynx the larynx and even the trachea down to the bifurcation may be affected The tonsils become ulcerated by confluent lesions The tongue is often relatively little involved The discomfort of the patient is not so much caused by the actual smallpox lesions on the mucosae as by the diffuse catarrhal inflammation which accompanies the enanthem This is particularly true of the nose and nasopharynx which often are obstructed by bloody crusts.

The conjunctiva bulbi is only rarely involved the conjunctiva palpebralis a little more often. Pustules may appear usually in small numbers in the vagina the rectum and the urethra.

The pustular stage at the middle of the second week represents the acme if the disease takes a normal course. From then on the edema of the face subsides and the pus at first in the facial lesions and then in the others in the order of their appearance becomes thicker and the areolae lighter. The pustules which were firm and shotty become flat and shrink. They form yellow crusts which finally become brown dry and loose. The pain subsides however a very annoying pruritus frequently accompanies the loosening and shedding of the scabs. The respiratory irritation subsides and at the end of the second week the temperature is again normal this time to stay. The healing pustules leave pigmentations and pitted scars of varying degree. The scarring may consist of a few pockmarks not much more severe than in some cases of varicella or it may disfigure the patient's face to the utmost for the rest of his life. Diffuse alopecia follows variola probably more often than it follows other exanthematic diseases. The hair grows back except in the few spots where pustules have destroyed the hair papillae.

The clinical picture of smallpox varies considerably with the epidemic and with the status of immunity of the patient. In addition complications may modify the course decisively.

In *variola confluens* as compared with variola discreta the pustules are so dense that they coalesce and form large superficial abscesses and infiltrations. All symptoms are aggravated. The face is most severely involved the trunk less so. The eyes cannot be opened the lips and the nose are swollen and crusty and the saliva runs from the mouth. According to an old clinical experience (Sydenham after Osler Christian[89]) the number of pustules on the face decides the outcome and a relatively mild eruption on the rest of the body does not make up for a dense and confluent exanthem on the face. Such confluent cases are sometimes, but not always heralded by severe lumbar pain in the initial stage and by a precipitate eruption on the second or third day.

Variola minor is a mild form of variola, with a sparse exanthem which does not always start on the face.[90] There is no initial rash and no second fever period. All symptoms run a mitigated and abbreviated course. Tièche[91] often observed a one- to two-day period without symptoms between the prodromes and the eruption. Very experienced authors believe that variola minor is a separate disease but others[92] propose a unitarian theory. Some of the arguments follow. No certain case of variola major stemming from contact with variola minor is known. Vaccination does not afford the same protection against variola minor as against variola major[93] although this is controversial.[94]

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[90] Immermann, H. Variola. Vienna, 1896, Alfred Hölder.

[91] Tièche, M. Epidemiologisches und experimentelles über Variola und Vaccine. Korresp. Schweiz. Aerzte. 1913.

[92] Obersteiner, O. Variola [illegible] Alastrim. Centralbl. f. Bakteriol. 110, 97-115 1 9-130, 1929.

[93] Van Campenhout, E. Considérations sur le diagnostic de variola major et variola minor. Bull. Office internat. d. hyg. pub. 27, 724-17, 1935.

[94] Kröber, F. Beobachtungen bei einer Epidemie von Alastrim. Deutsche med. Wchnschr. 60: 793-794, 1934.

Variola minor does not always immunize against vaccinia (see Sobernheim) The variola minor pustule is white and has several times been described as unilocular and not umbilicated [493] Such terms as alastrim amaas kaffir pox white pox and Cuban itch have been used to designate the epidemic variola minor It should be emphasized that if the mild character of a case of variola is due to the status of immunity for example preceding vaccination infections stemming from such cases may be severe The exanthem may fail to appear after the prodromal symptoms. Such cases of *variola sine exanthemae* are rare usually favorable but also contagious.

Hemorrhagic complications may create two distinct varieties of smallpox If purpuric symptoms appear in the prodromal stage if the initial rash is purpuric or petechial or if the mucosae show early petechiae or bleeding one speaks of purpura variolosa or hemorrhagic smallpox These patients die within a few days in some instances before the outbreak of the exanthem. Fulminating purpura discoloring wide areas may develop All who have seen such cases of black smallpox have been impressed by the ghastly appearance of the patient whose entire skin may be deep purple the face swollen the conjunctivae deep red and the gums bleeding

The term *variola pustulosa hemorrhagica* characterizes the cases with the appearance of hemorrhagic symptoms in the pustular stage. This too is a severe and usually fatal complication At first the halos then the pustules themselves become hemorrhagic. Osler[86] and other clinicians who have witnessed great epidemics of smallpox agree that the earlier the purpuric complications set in the more dangerous they are

The earlier clinicians[494] mention two rare peculiar cutaneous variation of the healing process. Sometimes a warty-looking crusty greasy mass may remain in the place of the pustule and only slowly become eliminated This is called wart-pox *variola verrucosa* Still rarer is *variola siliquosa* Here the content of the pustules disappears rapidly leaving for a while an air filled blister The gross pathology of the inner organs shows a surprising paucity of changes The histopathology of the early stages of the variola papule shows acanthosis with vacuolization and liquefaction around a center in the higher strata of the prickle-cell layer Here the multilocular vesicle develops The umbilication is caused by acanthosis which raises the edges higher than the liquefied center The navel may disappear if the chambers of the vesicle coalesce or become more distended The peculiar cell changes, described by Unna are identical with those in vaccinia (see under vaccinia)

The *diagnosis* is occasionally difficult. A secondary syphilid may though rarely imitate variola and one should search for other syphilitic signs or symptoms. Variola if modified by vaccination may resemble varicella. However chicken pox has no prodromes and the temperature does not drop during the eruption which appears in several crops predominantly on the trunk. The vesicle in varicella is very superficial and thin and can be wiped off while this is not possible with the deeper and more thickly walled smallpox lesion The areola (corona) in varicella is irregular and sometimes very wide while the halo around

the variola pustule is narrow and regular The shape of the varicella vesicle is often irregular even elongated in the body folds compared with the round circumference of the variola lesion. Deep-seated scabs on the palms are quite characteristic of smallpox. The shotty feel of variola lesions may be absent and may occasionally even be found in varicella In smallpox the axilla often remains free while it is a favorite spot for the eruption of chicken pox.[108] Morawetz[319] mentions unusually copious eruptions of erythema multiforme as being a possible obstacle to the diagnosis Here the emphasis of the distribution is on the extensor surfaces of the extremities not on the face. The prodromal stage the fever the contacts the preceding vaccinations and especially Paul's test the scarification of a rabbit's cornea with a needle dipped into the questionable lesion establishes the diagnosis (see vaccinia) In persons who have been sensitized by often repeated vaccination a skin test with sterilized material from the questioned eruption may be positive within four hours (Tièche after Paschen[89]) if the disease is vaccinia or variola.

No specific therapy is known The treatment is symptomatic. Vaccination at the time of exposure attenuates the outbreak of variola to an attack of fever without eruption A few days after exposure vaccination can still weaken the course but this is no longer true after the outbreak of the prodromes.

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[108] Fuller A. Differential Points in Diagnosis of Smallpox and Chickenpox, Ohio State M J 24 958-960, 1928

CHAPTER VI

SYSTEMIC INFECTIONS

Pinta

Pinta (mal del pinto carate) is a tropical disease characterized by unusual pigmentary changes and caused by *Treponema carateum* This treponema was discovered by Grau Triana and Armenteros in Habana Cuba in 1938 The spirochete for which at least six names exist (Treponema herrejoni pictor americana pintae dischromeoderma) is demonstrable in active lesions by the dark field examination or by the same stains which are used to detect *Treponema pallidum* from which it is morphologically indistinguishable For generations the disease was considered a mycosis. However the absence of fungi the high incidence of positive Wassermann and Kahn reactions (Menck [*] 60 per cent Herrejon and Pallares 100 per cent after Pardo-Castello and Ferrer[4] and the rapid response to antisyphilitic treatment made a spirochetal cause of the infection appear probable The disease is inoculable into normal and syphilitic persons but not into persons with pinta of the later stages (León y Blanco Beerman [*]) It is believed that the infection takes place by contact and not by a vector No venereal transmissions have become known The infection conveys immunity The disease occurs predominantly among colored races in the Latin American countries. About 600 000 sufferers are believed to live in Columbia and over 270 000 in Mexico [*] A few cases have been discovered among Negroes in Chicago [*]

Dermadromes —Mainly through the brilliant and heroic work of the Cuban dermatologists it is now known that seven to ten days after an inoculation of pinta material into the skin a minute *primary papule* with a red halo develops. Within two months this initial lesion gradually becomes an erythematosquamous patch surrounded by satellite papules which tend to coalesce with the primary lesion The primary patch may grow slowly to 10 to 13 cm in diameter and finally become indistinguishable from secondary lesions (pintids León y Blanco [*])

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[*]Menk W Percentages of Positive Wassermann Reactions Associated with Various Diseases, Fifteenth Annual Report of the Medical Department of the United Fruit Company New York 1926

[*]Pardo-Castello V and Ferrer I Pinta mal del pinto carate Arch Dermat & Syph 45 843-864 1942

[*]Leon y Blanco F Las queratosis palmares y plantares en el mal del pinto Rev de med trop y parasitol bacteriol clin y lab 6 167-184 1940 Estudio epidemiológico del mal del pinto en una pequeña aldea del estado de Guerrero México Rev de med trop y parasitol bacteriol clin y lab 6 195-200 1940 Las reacciones de Bordet Wassermann de Kahn en el período secundario del mal del pinto Rev de med Trop y parasitol bacteriol clin lab 6 201-205 1940 Nota sobre la evolución histórica de nuestros conocimientos acerca del mal del pinto carate Rev de med trop y parasitol bacteriol clin lab 6 249-302 1940

[*]Beerman H Pinta Etiology and Clinical Studies Am J M Sc 206 611-633 1943

[*]Fox H A Census of Mal del Pinto in Mexico Arch Dermat & Syph 31 227-229 1935.

[*]Lieberthal, E P Pinta in the Continental United States J A M A 123 619-621 1943

which appear five to twelve months, or more, after the infection A variety of pintids, characterized as trichophytoid psoriasiform lichenoid and eczematoid have been described The lesions are at first pink, then red purple and finally slate colored indicating the onset of the pigmentary changes which are so characteristic of the disease. The older secondary lesions often show a depressed



Fig. 34 —Pinta Typical triangular leukoderma of olar aspects of the rists (From Pardo-Castello, V Arch. Derma 1942)

center and an active raised margin. Coalescence of the lesions is a feature. The distribution becomes more and more symmetric and widespread and the pintids may involve any region although they are found mostly on the exposed areas and over the bony prominences. There are hardly any subjective sensations. In Mexico the early secondary stages were called *empeines*. They were thought to be a separate entity. Their relation to pinta has only recently been elucidated by León y Blanco[146] (see Pardo-Castello[147])

The secondary stage gradually passes into the *tertiary* or *dyschromic* stage with the spectacular pigmentary symptoms which have given rise to the name mal del pinto (Spanish pintar, to paint, meaning piebald disease). The first dyschromic lesions may appear after one year especially in symmetrical distribution on the hands, forearms, feet and lower legs. However the face, the trunk, and the scrotum may finally be covered with permanent vitiligo-like changes.



Fig. 85.—Pinta. Hyperkeratotic and dyschromic lesions of the palms. (From Pardo-Castello, V. Arch. Dermat. 1942.)

Especially characteristic is a depigmented area on the volar aspect of the wrist in the shape of a triangle with the base bordering the palm and the apex pointing toward the elbow. *Such lesions are composed of irregular sharply outlined* spots of hyperpigmentation which in white persons who are rarely affected varies from yellow to brown and in colored person from brown to slate-blue and black, the center being white. Pardo-Castello[47] emphasizes the pepper and salt or mottled arrangement of the pigmented lesions. The discoloration may be found accompanied by follicular and diffuse keratoses and areas of atrophy

The Wassermann is always positive in this stage. The white patches represent the final stage and do not respond to antisyphilitic treatment which is effective in the other lesions.

The general health seems little affected during this extremely chronic disease which may last several decades. However it is likely that, as in syphilis more internal manifestations will be discovered Already a high percentage of late cardio-aortic lesions and spinal fluid changes have been reported [illegible]

The initial and secondary lesions show essentially the same *histological* changes, that is, edema of the rete and inflammatory infiltration. The great disturbance of the pigmentary physiology is expressed by the lack of pigment in the basal layer and great accumulations of melanophores in the cutis. Spirochetes are numerous only in active lesions. Late lesions become increasingly atrophic.

The differential diagnosis includes syphilis yaws, vitiligo leprosy and certain dyschromic conditions. Seroreaction the finding of spirochetes and the effect of specific treatment will help However the differentiation from syphilis and yaws will rest mainly on the clinical appearance. The effectiveness of the same treatment in all these diseases reduces the practical importance of the differential diagnosis.

Frambesia (Yaws)

Frambesia is a tropical spirochetosis closely related to syphilis although different in many ways. The word frambesia, derived from the French framboise, raspberry refers to the red papillomatous lesions which are a conspicuous feature. The disease is called yaws in English le pian in French and la boubarole or boubas in the Caribbean area. The causative agent is *Treponema pertenue* a spirochete which is morphologically indistinguishable from *Treponema pallidum*. The infection is endemic among the lower classes of all tropical countries the incidence depending upon the unsanitary conditions rather than on the race Contrary to a widely held belief that frambesia is predominantly a disease of the colored population it is certain that poor living conditions cause a high percentage of infections among the white population [illegible]

Transmission occurs chiefly by direct contact The fly Hippelates pallipes, culex mosquitos, or leeches possibly play roles as mechanical vectors. Venereal contagion is extremely rare due to the infrequence of superficial mucosal lesions. However penile primary lesions have been observed[illegible] and are even considered very common in the Cameroons.[illegible] Congenital infection is questioned by many authors, although claimed by some Infection with yaws seems to immunize against syphilis.[illegible]

The *incubation* period lasts two to three weeks, during which time mild febrile prodromes often occur

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[illegible] Saenz, B Trinas, J and Armenteros, J Pinta in Cuba, Arch. Dermat. & Syph. 41: 463-479 1940.

[illegible] Pardo-Castello V Frambesia, 400 Cases, Arch. Derma & Syph. 40: 762-778, 1939.

[illegible] Mayer M. and Nauck E G Framboesie Handb d. H. u. Gk. 13: 857 1932.

[illegible] Hallenberger Frambesia, Arch f Schiffs u. Tropen Hyg 20: Beiheft 2, 1916.

[illegible] Fox, H Skin and Tropical Diseases, New England J Med. 231 482-488, 1944.

Dermadromes.—The *primary lesion*, called the mother yaw, appears usually on the exposed parts of the legs, or much less frequently elsewhere. The initial sore starts as a papule or pustule which soon becomes granulomatous or ulcerative. Such lesions may disappear or become inconspicuous among the great number of almost identical secondary lesions. In a considerable number of cases the primary lesion keeps on growing and develops slowly into an enormous destructive ulcer. Such "mother yaw" lesions have been seen to remain active as long as twenty years. They may heal with a scar in any stage or may extend peripherally and deeply even to destruction of the underlying bones.[443]



Fig. 56.—Y. Early papulohyperkeratotic plantar lesions. (From Pardo-Castello, V.: Arch. Dermat., 1939.)

Multiple primary lesions and the appearance of satellite papules around the sore are well known.

From six to nine weeks after the infection, the *secondary eruption* appears. This is a papular rash, often ushered in by prodromal symptoms like fever, muscular pains, and headache. There is a generalized lymphadenopathy (Baermann

after Mayer and Nauck[illegible]) The secondary exanthem has a peculiar tendency to develop luxuriant papillomatous lesions. These efflorescences may be generalized, grouped about the body orifices numerous or scanty small or large. They may appear as miliary pin point sized elements as impetigo-like crusty lesions or as raspberry like papillomatous granulomas.[illegible] Most of the secondary lesions disappear but groups of papules arranged in rings (ringworm yaws) or in lichenoid plaques persist during the late secondary period The soles are often covered with symmetric, deep cornlike painful papules which are surrounded by keratotic eczematoid scaly skin (crab yaws) (Fig 56) The truly granulomatous and frambesiform nature of such plantar lesions becomes evident after removal of the thick horny top layer [illegible] On the palms such lesions may look psoriasiform. Areas of mottled pigmentation and depigmentation on the hands and feet may create a picture which closely resembles pinta[illegible] (Schüffner s p cture in Mayer and Nauck[illegible])

The *tertiary* lesions are seen earlier than in syphilis. A period of late secondary latency is rare. As in syphilis the late lesions may be ulceroserpiginous sometimes of enormous size with a nodular border and a scarred center or deeply destructive and granulomatous. They may destroy joints and bones and cause pathological fractures Particularly horrifying are the facial and nasopharyngeal mutilations known as *gangosa* which may cause complete loss of the nose and may extend to the lips and lay open the nasal and oral cavities Later on scarring may cause microstomia and the hands, under similarly destructive and cicatrizing processes may become monstrously deformed and mutilated Pardo-Castello[illegible] emphasizes the bone destructive tendency of yaws in contrast to the more osteoplastic nature of the corresponding syphilitic processes.

There is remarkably little involvement of the mucous membranes Destruction of the soft palate is rare and cardio-aortic and cerebrospinal changes are infrequent.[illegible]

The pathology of yaws largely follows the pattern of syphilis The proliferative tendency of the papules, which in syphilis manifests itself in the condylomata is much exaggerated in yaws.

Yaws apparently renders the patient immune, and there seems to be some degree of cross immunity in the later stages of syphilis and yaws.

Treponema pertenue is demonstrable in many of the lesions and occasionally in the late gummatous processes which in syphilis is only extremely rarely the case. Wassermann Kahn and the related reactions are positive in 100 per cent of the secondary cases less often in the later stages.[illegible] The disease is inoculable into monkeys and like syphilis into the anterior chamber of the rabbit s eye and into the testicles of the rabbit.

The treatment is largely the same as for syphilis with the emphasis on the arsphenamines and bismuth Mercury and iodine are reported to be unsatisfactory Oral arsenicals for example acetarsone are effective and convenient

[illegible] Schüffner W Die Spirochaeta pertenuis und das klinische Bild der Framboesia tropica, München med Wchnschr p 1364, 1907

under primitive conditions.[illegible] The treatment consists of daily doses of 0 25 Gm for twenty days. These courses are repeated several times after intervals of two weeks. Penicillin has shown promising results [1]

Juxta articular Nodes

Subcutaneous movable pea to walnut sized or occasionally much larger nodules of firm or hard consistency occur on the extensor and lateral surfaces of the elbows, knees and other joints.[illegible] They grow slowly for years usually sym



Fig 87 —Juxta-articular nodes (Courtesy of Di ision of Derma ology Department of Medicine U iversity of Chicago)

metrically often multiple never in large numbers. The lesions called juxta articular nodes, are tender in the first years of their development but later are painless and stationary There is no tendency to ulcerate or to heal spon taneously *The affected are as a rule elderly persons.*

[illegible] Whi hill and Austrian Trea men of Y ws With Penicillin, Bull Johns Hopkins Hosp. 75 233-240 1944

[illegible] Zakon S J and Allen H J ta-Articular Nodes, Quart Bull Northwestern Uni Med School 14 270-273 1940

The *pathologic* picture [illegible] (Jeanselme after H Hoffmann [illegible]) is that of a cyst with a thick, fibrous vascular outer wall in which perivascular inflammatory reactions with foreign body type giant cells and proliferation of blood vessels dominate Toward the center of the cyst the inflammation subsides the elastic fibers deteriorate and the nuclei lose their stain The center is a mass of hyalin or liquid degenerated material.

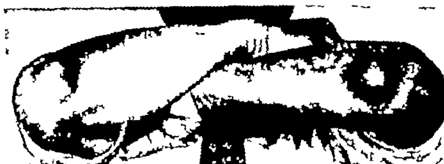


Fig 55 —Syphilitic juxta-articular nodes. (From Kalz, F Arch Dermat 1943.)

The nodes are ra e in temperate zones and common in the tropics. This is due to the fact that the tropical treponemal diseases especially yaws [illegible] but also syphilis [illegible] pinta,[illegible] and bejel [illegible] are apt to cause juxta articular nodes in their later stages Spirochetes were demonstrated regularly in the nodes of thirty six patients with frambesia [illegible] Patients with active lesions should receive antisyphil tic treatment.

Besides the treponemal diseases several disorders, particularly chronic arthritis may sometimes cause typical juxta articular nodes [illegible]

Relapsing Fever

A group of relapsing fevers is characterized by attacks of severe acute fever lasting two to ten days [illegible] The causative organism *Borrelia recurrentis* (*Spirochaeta obermeieri*) discovered in 1868 is a very large spirochete about six times the length of the diameter of a red blood cell and is found in great numbers in the blood during the attacks. It is transmitted by lice bedbugs (Tictin after Eggebrecht[illegible]) and ticks [illegible] probably not by bite but by inoculation from the crushed nfected nsect body with the scratching nail There are a number of

[illegible] Jeanselme M Ueber syphilitische juxtaartikuläre Knotenbildungen, Arch f Dermat u Syph. [illegible] 123-147 [illegible]

[illegible] Kalz F and [illegible] D L Syphilitic Juxta-Articular Nodules Arch. Dermat. & Syph. 48 [illegible]

[illegible] Hudson E H [illegible] and [illegible] Am J Trop Med 21 [illegible], 1941

[illegible] Van Dyk and [illegible] [illegible] Histology and Cause of Juxta-Articular Nodes, [illegible] Nederl Indië [illegible]

[illegible] Arewiak A and [illegible] [illegible] Infection and Syphilitic Juxta-Articular Nodes, [illegible] Dermat [illegible]

[illegible] Eggebrecht E Febris recurrens Vienna 1902 Alfred Hölder

[illegible] Schilling C Rückfallfieber in Handbuch der inneren Medizin, Vol [illegible] Berlin, 1925 Julius Springer

geographic varieties of relapsing fever differing in vector duration and number of attacks The relapsing fevers are important in Europe and Africa less so in America where there are some endemic foci in California and Nevada [147] The first attack starts abruptly after one to seven days of incubation There may be prostration often vomiting cough splenomegaly and increasing anemia. The attack ends by crisis and the patient recovers remarkably quick but after one to two weeks he has another though often milder attack. Such bouts may recur two three or even five times. The prognosis is good the fatality rate in most epidemics is less than 5 per cent.

Dermadromes.—Dermadromes are inconspicuous and inconstant. There is a decided icteric tendency which together with the increasing anemia may create a dirty grayish-brown color This facial browning was emphasized by the older authors[148] (McCormack after Eggebrecht[148]) With varying frequency in different epidemics, rose spots similar to those in typhoid morbilliform and very rarely scarlatiniform and miliary rashes[148] have been noticed The relapsing fever roseola is described[149] as appearing at the end of the first attack most frequently on the lateral surfaces of the trunk, on the back on the extensor surfaces of the elbows and about the wrists. Face and legs remain free The spots are smaller than those in typhoid round purely macular and pink to red in color They fade after about one hour but since they do not appear simultaneously these spots are visible for a much longer period The exceedingly ephemeral character of the spots is stressed by other authors.[314] In ten years of experience with American relapsing fever in Nevada Parsons did not notice any rashes (personal communication)

Since the diagnosis rests on the finding of spirochetes in the blood the infrequent exanthems are hardly of diagnostic importance The usual symptoms accompanying profuse *sweats* sudamina and mild desquamation are common. *Herpes* was noticed in up to 30 per cent of the cases in certain epidemics. *Petechiae* (which should not be confused with flea bites) and other hemorrhagic symptoms especially nosebleed occur[314] occasionally especially at the end of the attack. It is interesting that the acumen of the older clinicians did not fail to notice that patients with relapsing fever usually show the excoriations pigmentations and pyodermatic infections connected with chronic pediculosis and neglect a state known as *vagabond's skin*

Specific treatment consists of a few injections of arsphenamine

Weil Disease (Leptospirosis Ictero-hemorrhagica)

Weil's disease (*Leptospirosis ictero-hemorrhagica*) is an acute spirochetal infection with fever gastrointestinal and hepatic symptoms and prostration After five to six days of high temperature a large percentage of the patients become jaundiced and hemorrhagic tendencies become manifest The mortality

[147] Morrison S K and Parsons, L Relapsing Fever J A M A 116 220-22 1941
[148] Strong R P Relapsing Fever Cli North America 27 721 744 1943
[149] Oettinger J and Halbreich J Ephemere Roseola beim Rückfallfieber München med Wchnschr 691 778-779 1922

amounts to about 12 per cent with most of the deaths occurring around the end of the second week.

The causative spirochete is found in the blood

Dermadromes —Frequent skin manifestations include icterus and hemorrhagic lesions. Scarlatiniform urticarial[440] and other types of rashes are rare. Non angry endogenous bulbar conjunctivitis and episcleritis are considered early and striking symptoms.[441]

There are *milder varieties of Leptospirosis* for example the so-called inundation or mud fevers in Germany in which *morbilliform* rashes occur[8, 442]

Ratbite Fever (Sodoku)

There exist two clinically similar diseases which develop in man after the bite of rats but which are attributed to different microorganisms. One of these, caused by *Streptobacillus moniliformis* has been discussed under the heading Haverhill fever Under the name of sodoku which in Japanese means poisoning by a rat the other has been known for centuries only in Japan although it is as cosmopolitan as the rat. Simultaneous infection with both microorganisms occurs.[443-444]

The cause of sodoku *Spirillum minus* (formerly *spirochaeta morsus muris*) was discovered in 1917[445] It is a fast moving spirochete having only two to five spirals and shorter in length than the diameter of a red blood cell There are flagella at both ends (B McDermott after Beeson[446])

A great number of cases with the spirillum present, have been reported from many countries. In a great number of the cases, children were affected[447] Epidemics are not known. The disease is rare, one case being recorded among 20 000 hospital admissions in Kansas City Yet because of its wide use in the treatment of general paresis, the symptomatology of the disease is well known

Spirillum minus is harbored by rats, especially the vicious *rattus norvegicus* but also in a host of other rodents, and occasionally by cats and dogs. White mice and guinea pigs are susceptible to laboratory inoculation Animal inoculation with blood taken at the height of a febrile paroxysm is the most reliable method of demonstration[8] No pure cultures have been grown so far The organism may occasionally be demonstrated in the serum from a primary lesion in a local lymph node or in the blood[8] with the help of the dark field or with

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[440] Lorenz, O J Studies in Weil Disease U S N M Bull 42 560-568, 914.
[441] Kathe J Schlammfieber Erntefieber Wasserfieber Feldfieber Infektion durch Leptospiren, Med Klin. 35 1123-1128 1939
[442] Rimpau, Feldfieber München med. Wchnschr 85 1977 1979 1938.
[443] Nathan, H Rattenbisserkrankung, Kbl Chir pp 757-758 1933
[444] Anderson N P and Spector D K Rat Bite Fever Associated With Sporotrichosis, J Infect. Dis. 50: 314-319 1932
[445] Futaki, K Takaki, T Taniguchi, T and Osumi, S The Cause of Rat-bite Fever J Exper Med 23: 2 9-230 19 6
[446] Beeson, P B Rat-bite Fever Due to Spirillum Minus, J A.M.A 123 332-334, 1943.
[447] Brüning, H Sodoku Rattenbisskrankheit) bei Kindern, Ergebn. d. inn. Med. u. Kinderh. 41 1-44 1932
[448] Francis E Rat-bite Fever and Relapsing Fever in the U S A., T A. Am. Physicians 47 143-151, 1932
[449] Roughton, A O Two Cases of Rat-bite Fever Surgery 11 433-438 1943

stains used for spirochetes. Inoculation of mice is more likely to yield results than microscopic procedures, although the accidental occurrence of spirochetes must be ruled out

The incubation period varies from two to thirty-six days with the greatest frequency between seven and twenty-one days[illegible] The outbreak of the disease is often preceded by malaise headaches loss of appetite and muscular pains.

Dermadromes —The bite wound which is usually healed at the outbreak of the disease changes into a *primary lesion* which may become an indurated and wide ulcer with steep edges necrotic floor and angry bluish red surroundings.[illegible] In some cases the primary chancre is marked only by a blister (Knowles and Das Gupta after Breinl[illegible]) or it may be absent. The local lymph nodes are swollen and tender Later generalized *adenopathy* develops. Acute high fever with chills accompanies the first attack which lasts several days and is almost regularly accompanied[illegible] by a rash It should be emphasized that in only 20 to 25 per cent of the cases of sodoku which were induced for treatment of general paresis did a *rash* develop[illegible] (Teitelbaum after Brown and Nunemaker[illegible]) This rash may start as a livid erythema around the infected wounds[illegible] and spread to other parts Erythema multiforme like papulo-urticarial or macular rashes as well as (Taccone after Brüning[illegible]) livid *erythematous plaques* up to 14 cm in diameter with or without induration and sometimes with a pale center are common These lesions are usually not symmetrically distributed[illegible] (Knowles and Das Gupta after Breinl[illegible])

Petechial pustular and morbilliform exanthems in sparse or copious dissemination over the entire body only about the joints or in isolated areas have also been observed A papular eruption in the mouth may occur[illegible] A peculiar feature is an acute episode of *urticaria* which occurs shortly before the end of the attack (Miyake after Brown and Nunemaker[illegible]) Sometimes severe muscular pains nausea and vomiting dominate the picture Edema of the lower legs especially around large indurated plaques[illegible] is a frequent feature[illegible] and is considered to be of unfavorable prognostic significance Leukocytosis is marked Attacks with flare-ups of the primary lesion as well as of the rash and the other symptoms may recur at intervals of about five days The number and severity of these relapses vary from six to ten or even more but the bouts generally become milder as immunity develops. The relapsing character of the disease is not always evident since it may consist of prolonged periods of sustained or of daily intermittent fever producing a great variety of clinical pictures Without specific treatment the disease may pass into a chronic stage

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[illegible] Breinl F Die Rattenbisskrankheit Handb d H [illegible] Ok 13, 1 [illegible] 1933

[illegible] Veen, H Rattenbisskrankheit Nederl tijdschr geneesk 75 [illegible] 1931 Zbl 37 [illegible]

[illegible] Hershfeld H Kiebler O A Colby Y Koenig M T Schmidt O W and Saunders A M Sodoku Treatment in Paresis J A M A [illegible] 772-773 1929

[illegible] Mellerson E Ueber Rattenbisskrankheit H [illegible] 1929 Zbl 32 [illegible]

[illegible] O'Leary P A The Dermatologic Aspects of Rat-bite Fever Arch Dermat & Syph 9 [illegible] 1924

[illegible] Kandern I Ein Fall von Rattenbissfieber Sodoku Ugesk f laeger 99 [illegible] 1937 Zbl 57 [illegible]

[illegible] Wolf H de Rat-bite Fever Arch Dermat & Syph 25 772 774 [illegible]

In some cases, severe sensory or motor nervous symptoms prevail Diffuse and patchy *alopecia* has occurred in later stages. The hair grew back after general improvement.[illegible]

The *Wassermann reaction* and related tests become positive in 50 to 60 per cent of the cases [illegible]

The mortality of the treated patients is low No fatality occurred among 125 cases reported in the United States.

The clinical diagnosis must take into account a great many fevers, although the history of a ratbite, the primary lesion and the laboratory findings will secure the diagnosis. The differentiation from rat bite transmitted Haverhill fever is made by the laboratory findings[illegible] as well as by the presence of arthritis and the lack of a pronounced primary chancre in Haverhill fever Haverhill fever after ratbite is probably more common than sodoku.

Specific *treatment* consists of from three to ten injections of neoarsphenamine or similar arsenicals. Bismuth is also effective.[illegible] The first administration of specific drugs may be followed by a Herxheimer reaction [illegible] Recurrences have been seen after less than three injections.

The *therapeutic inoculation* of the disease into patients with general paresis instead of malaria was done in a great number of patients, but has been abandoned because complications occurred and control of the infection often proved difficult.

African Trypanosomiasis

The trypanosomiasis of central Africa (sleeping sickness)[illegible] is caused by the flagellates *Trypanosoma gambiense* and *Trypanosoma rhodesiense* These microorganisms are blood parasites of many wild and domesticated large mammals for example oxen sheep, and antelopes, and are transmitted to man by the bite of the tsetse fly *Glossina palpalis* The transmission is cyclical and mechanical. The trypanosomes are most abundant in the blood during the febrile attacks, but they are also found in the lymph nodes, the cerebrospinal fluid and serous fluids They can be stained demonstrated by dark field and cultivated on salt agar (NNN medium)

The disease is endemic and at times epidemic, in large parts of equatorial Africa especially around lakes and along rivers where the tsetse fly lives. At times the population of large areas is decimated by the disease which affects the colored races as well as the white. The infecting bite is often immediately or within one week,[illegible] followed by local inflammation These primary chancres do not develop invariably but furunculoid and ulcerative lesions, with regional

[illegible] Castellani, A Rat-bite Fever Proc Roy Soc Med 27: 1578, 1934

[illegible] Ozeki, Y Die Rattenbisskrankheit Impfungsmethod des Erregers, Jap. J Dermat & Urol. 33: 46 1933 Ibid 42 494

[illegible] Manson-Bahr P H Manson Tropical Diseases, London, 1936 Cassell & Co Ltd.

[illegible] Kellersberger E R African Sleeping Sickness, M Clin North America 27 833-847 1943.

[illegible] Mayer M Hauterscheinungen bei exotischen Krankheiten Trypanosomiasis, Handb d. H Gk 12, 1 180-184, 1932

[illegible] Graf H Beitrag zur Pathologie der Glossina palpalis-Stiche und der Inkubationszeit bei Schlafkrankheit, Arch f Schiffs- u Tropen-Hyg 33: 510-522 1929

lymphatic involvement fever and the local presence of the trypanosomes have been observed beyond doubt.[[illegible]] About two to three weeks after the infection the patient is stricken with fever of varying intensity and course the



Fig 59—African trypanosomiasis Secondary exanthem (From L Owen, courtesy The Annals of Tropical Medicine and Parasitology The University Press of Liverpool)

irregularity being a diagnostic feature [[illegible]] The patient becomes weak and anemic and his mental abilities suffer General lymphadenopathy is a constant though varying feature with the lymphatic nodes at first being soft later hard Head

[[illegible]] Géry L R Les phénomènes cutanés au cours de la trypanosomiase humaine en particulier dans la race blanche Thèse de Paris 1910

aches, paresthesias, and a peculiar kind of deep hyperesthesia on knocking against a hard object known as Kerandel's sign indicate the early nervous involvement.

Dermadromes.—The primary lesion has a deep red center surrounded by a pearly white vesicular zone and a red halo.[553] Erythema and infiltration around the bite may persist far into the secondary stage. The bite however differs in its appearance from the more transitory *secondary eruptions*.[554-556] Characteristic of the early secondary stage but not present in all patients nor at all times,[554] are *urticarial erythemas* in large round patches rings, or crescents which have a decided tendency to spread peripherally and heal in the center. Coalescing circinate rather large patterns may cover the entire back.[555-557] These trypanids are of unpredictable and fugitive nature. They may be without change for days or even several weeks and then they may evanesce quickly reappearing in other places. The erythemas are slightly raised but not or little infiltrated,[554-556] pink in color of normal temperature often sensitive and sometimes very itchy especially if they are of a more exudative papular type.[556] Erythema nodosum occurs.[557-558] The blood taken from lesions contains more trypanosomes than the peripheral blood of the other skin. The relatively delicate erythema is difficult to detect in colored skin. In some cases the erythema is annular and linear[558] like the erythema annulare encountered in rheumatic fever.

Localized edema especially of the face is common in the secondary stage.[555-556] Another dermadrome is a vascular bluish mottling independent of the erythemas (Master after Mayer[551]).

The fading skin lesions do not leave any trace.[556] The secondary stage may last a long time seven years usually being considered the maximum. The skin manifestations become less marked and less frequent and gradually the disease drifts into the sleeping sickness stage with deep mental changes, stupor and somnolence during daytime restlessness at night muscular twitchings tremor and convulsions. Hepato-splenomegaly is present. If not treated death in profound cachexia is inevitable.

During the *encephalitic* stage early features, including erythema may still be present. The gross pathology is meager. Microscopically perivascular round cell infiltrations can be seen throughout the brain and especially in the erythematous skin.[556]

The *diagnosis* rests on the finding of trypanosomes in the blood in the lymph node material or in the spinal fluid. The clinical diagnosis of trypanosomiasis

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Dr Kellersberger of the American Mission to Lepers, who has had an almost unique experience with African trypanosomiasis does not believe that the rashes are very commonly seen, since most of the patients in the treatment centers have advanced cases and the colored skin makes the erythemas difficult to observe (personal communication).

[554] Ruge, H. Sleeping Sickness, Med. Welt, 13: 1444-1446, 1939.

[555] Chevallier P and Lévy G. Les trypanides éruption précoce de la maladie du sommeil, Bull Soc franç de dermat et syph 38: 185, 1931.

[556] Darré H. Les symptomes cutanés de la trypanosomiase humaine. Ann de dermat et syph 5: 673, 1904.

[557] Owen, D U. Clinical Notes. Trypanosomiasis, Ann Trop Med 21: 47-83, 1929.

[558] Audry C. Erythème annulaire centrifuge et trypanosomiase, Bull Soc franç de dermat et syph 39: 188-190, 1932.

may be extremely difficult especially in persons who have moved from Africa to other countries. The large erythemato-urticarial centrifugal and annular erythemas are a most valuable sign. Together with internal manifestations they are almost diagnostic. Arsenic as tryparsamide pentamidine (M & B 800) and naphuride (Baeyer 205 germanin) are considered of high value.

American Trypanosomiasis (Chagas Disease)

American trypanosomiasis is caused by *Trypanosoma cruzi* and transmitted from infected persons and reservoir animals (armadillo opossum) by various species of *Panstrongylus triatoma infestans* and other bugs.



Fig 60 —Chagas disease Primary lesion (inoculation chagoma, fourteenth day) (Courtesy Mision d Estudios d Patologia Regional Argentina, Jujuy Argentina)

Skin Manifestation have long been considered of little importance. Recently however Mazza and his associates[139-146] demonstrated their significance

[139] Mazza, S and Freire R. Manifestaciones cutáneas d inoculacion (Chagomas) y hematógenas en enfermedad de Chagas. Universidad Buenos Ayres, Mision de Estudios de Patologia Regional Argentina Jujuy) Publicacion 46 pp 3-57 1940

[140] Mazza S and Urcelay G. Chagoma de inoculación, seguido de esquizotripanide morbiliforme. Ibid Publ 46, pp 58-61 1940

[141] Mazza, S and Miyara, S. Chagoma d inoculacion y esquizotripanide polimorfa. Histopatologia, Ibid Publ 46, pp 68-101 1940

[142] Mazza, S Basso G Basso R and Cos D. Chagoma antibraquial chag multiples metastaticos y hematogenos y complejo oftalmoganglionar. Ibid Publ 46, pp 103-11 1940

[143] Mazza, S Basso G and Basso R. Chagomas hematógenos, Ibid Publ 45 1940.

[144] Mazza, S and Jörg M E. Chagoma experimental, Ibid Publ 47 1940

[145] Mazza S and others. Investigaciones enfermedad d Chagas Ibid Publ 43 1940

[146] Mazza, S. Esquizotripánides alérgicas tardías en enfermedad de Chagas y otras manifestaciones eruptivas, Ibid Publ 71

[147] Mazza, S and Aranda, C A. Fuerdl ersuche bei der amerikanischen Leishmaniose Arch f Schiffs- Tropen-Hyg 35 453-461 1931

in a series of important investigations A primary skin lesion may appear as a large dark red prominent and deeply infiltrated nodule with or without intact epidermis (Inoculation Chagoma) which is histologically characterized by fat necrosis. Lymphangitis follows the primary lesion The inoculation often occurs on the face especially about the eye Thus, the first symptom often is a bipalpebral unilateral edema with conjunctival injection This eyelid edema lasts about four weeks (Romaña's sign)



Fig. 61.—Chagas disease Unilateral and bipalpebral edema and conjunctivitis. (Romaña's sign.) About three weeks after infection. (Courtesy Mision de Estudios de Patologia Regional Argentina, Jujuy Argentina.)

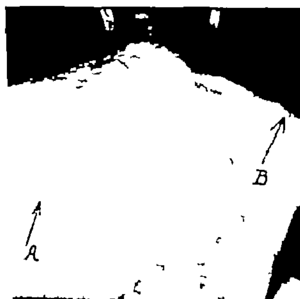


Fig. 62.—Chagas disease Rash five days old (Courtesy Mision de Estudios de Patologia Regional Argentina, Jujuy Argentina.)

As early as five days after the infecting bite a papular rash in the neighborhood of the bite a generalized circinate morbilliform or scarlatiniform erythema and cutaneous and subcutaneous nodules some of large size have been observed These nodules are very firm and deep red if they arise from the more superficial strata. Mazza also describes impetiginous and ulcerative eruptions seen several months after the infection



Fig 63 —Chagas disease Rash 8 days old (Courtesy Mision de Estudios de Patologia Regional Argentina, Jujuy Argentina)

Since the thyroid is often affected in the later stages dermadromes which occur in myxedema may be encountered *Edema* of the face and skin and also *bronzing* are mentioned The South American authors consider treatment with Bayer 7602 of great value but the drug the formula of which is secret still lacks general recommendation because of the danger of nephritis.[14]

A skin test with a cruzin has been developed The diagnosis however rests mainly on the microscopic and cultural evidence of trypanosomes in the patient s blood

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Mayer and Pifano Abstracted J Trop Di Bull 40 290 1942

[14] Mackie Th T Hunter G W and Brookes Worth C A Manual of Tropical Medicine Philadelphia, 1945 W B Saunders Company

Leishmaniasis

The leishmanias are flagellated protozoans which are capable of producing a group of diseases which are all of dermatological interest. Two of them oriental sore and American leishmaniasis (espundia) and possibly a third disease tropical granuloma inguinale are predominantly skin diseases and therefore will not be discussed. *Visceral leishmaniasis* or *Kala-azar* however is an internal disease with specific skin manifestations. It occurs in an infantile and in an adult form which are closely related.

The causative protozoan is a small ovoid or round body found either free or in cells of the reticulo-endothelial system particularly in the spleen the liver and the bone marrow In cultures on blood or salt agar (NNN medium) they assume the characteristics of flagellates and are inoculable into dogs and monkeys. The disease is endemic in the Mediterranean and the Near and Middle East especially in India which has been visited by great epidemics. Sandflies (Phlebotomus) are now considered as vectors with dogs as a reservoir particularly in the Mediterranean area



Fig. 61—Post-kala-azar dermal leishmaniasis in an incompletely treated case of visceral kala-azar. Depigmented nodules over the nose (Courtesy Dr S. K. Ghosh Dastidar)

The incubation period is over ten days long latency may occur Mirzoian[illegible] claims to have found the primary lesion in inconspicuous lentil-sized papules on the faces of children who several months later showed secondary symptoms of infantile kala-azar The lesions which contain leishmanias, may still be present at the time of the outbreak of systemic symptoms or they may have healed and left pigmented spots. The onset is insidious or abrupt with spiking fever which

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[illegible] Mirzoian, N. A. Primary Lesions of Visceral Leishmaniasis in Children. Trop. Dis. Bull. 40: 295-296, 1943

may last many weeks. Then an afebrile period with improvement may occur followed by a relapse of fever After several attacks a chronic state of emaciation low temperature and anemia becomes established. Gradually *the liver and spleen enlarge* to tremendous size—the big protruding abdomen contrasting sadly with the thin limbs. The appetite remains good for a remarkably long time Unusually low leukopenia and later ascites and edema are common Death is caused by cachexia or intercurrent disease for example dysentery or noma. The microscopic *pathology* shows abundant leishmanias in the reticulo-endothelial system.

Dermadromes.—The skin gradually takes on a claylike gray or dusky color *especially on the hands and feet* *This mixture of pallor and pigmentation* is seen in white as well as in colored races.[141] The dusky color accounts for the

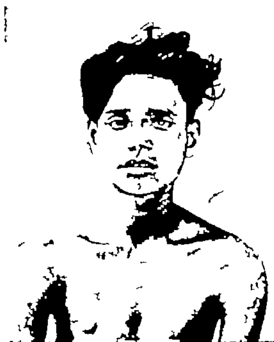


Fig 65



Fig 66

Fig 65 — *Post-kala-azar dermal leishmaniasis in a person of dark complexion.* *Small nodules on the* partly depigmented area on the chin, from one of which Leishmania donovani could be demonstrated in the smear Sharply defined depigmented spots are scattered over the chest, shoulders and face Patient had visceral kala-azar one year ago and was treated with 7 Gm of urea-stibamine, which is much less than the therapeutic dose (Courtesy Dr S K Ghosh Dastidar)

Fig 66 —Noma as a complication of kala-azar Sternal puncture smear showed Leishmania donovani (Courtesy Dr S K Ghosh Dastidar)

name kala-azar meaning black fever Petechiae and other hemorrhagic lesions, especially bleeding gums are common With the progressing cachexia small ulcerations about the elbows and knees and occasionally larger ulcerations along the legs may develop Specific papules and gangrenous ulcers containing leish

mania occur [illegible] as well as secondary cachectic ulcerations, such as noma. A most interesting cutaneous form of kala-azar[illegible] has become known as the *post kala-azar leishmanoid*. Eighty per cent of the patients were known to have had kala azar and to have been treated with antimony. Of the rest (Napier after Mayer[illegible]) a previous kala-azar infection could be assumed. The eruption starts with erythematous or depigmented patches on the face, especially about the nose and mouth. Such macules, resembling leprosy, may later appear on the limbs and on the trunk (see colored illustrations in M. Mayer[illegible]) but the chin, the upper lip and the eyebrow region are most frequently and most heavily involved. The macules are often followed by nodules which, however, may also appear first. These nodules are pea-sized or a little larger, semiglobular, firm, nonulcerating and covered with atrophic skin. Their color at first is red, later becoming decidedly orange. They may coalesce and form ridges of tuberous lesions, which resemble xanthoma tuberosum multiplex. The nodules contain only few leishmanias, mostly in giant cells in the center of a granuloma consisting mainly of macrophages and fibroblasts. The hypothesis has been advanced that some, possibly antimony fast, leishmanias remain in the skin and cause the local recurrences.

The *diagnosis* of kala azar may be suggested by the geographical location and the resistance of the fever to quinine. The finding of leishmanias by splenic or sternal puncture is diagnostic.

Kala azar is *treated* with antimony compounds. The post kala azar leishmanid does not respond well to this drug. It may become arrested in the late xanthomatoid form and remain without changing.

Malaria

There is no cutaneous lesion invariably or even frequently connected with malaria. Physicians of malaria free countries are inclined to visualize the malaria patient as having a sallow skin. This is only occasionally true. In countries where malaria occurs usually a high percentage of the population is infected and suffers from attacks. However, the typical *malarial color*, a dirty yellowish brown sallow hue, which in relatively rare instances may gradually take on deeper shades with a greenish component, is rare. The yellowish discoloration is more pronounced immediately after an attack and may approach a bronze shade as in blackwater fever.

Diffuse discoloration of the skin in malaria may be due to anemia from the destruction of the erythrocytes, to icterus, or to hyperpigmentation. Occasionally melanemia caused by large amounts of free malaria *pigment* in the blood serum may influence the skin color. The hyperpigmentation may compare with

[illegible] Shapiro, Y. M. and Dresh, S.: Kala-Azar in Palestine: Case With Cutaneous Lesions, Tr. Roy. Soc. Trop. Med. & Hyg. 33: 257-262, 1939.

[illegible] Acton, H. W. and Napier, L. E.: Post-Kala-Azar Dermal Leishmaniasis, Indian J. M. Research 15: 97-106, 1927.

[illegible] Brahmachari, U. N.: A New Form of Cutaneous Leishmaniasis—Dermal Leishmanoid, Indian M. Gaz. 57: 125-127, 1922.

[illegible] Napier and collaborators: Post Kala-Azar Dermal Leishmaniasis: A Series of Publications, Indian M. Gaz. 1929 and 1930.

addisonism in intensity and distribution including oral manifestations Racial pigmentation of the gums can be ruled out by the effect of specific treatment which however removes malarial pigment deposits but slowly Many authors have suggested that the adrenal cortex plays a part in the formation of the cutaneous pigment in malaria and there is some pathological evidence to support the clinical facts F Rosenthal and Löwenthal[144] found in such a case almost complete atrophy of the adrenals. Two types of pigment occur in the skin. The



Fig 67 Malaria tropica chloasma periorale and butterfly-shaped pigmentation over the cheeks Similar pigment lons has been described in bilharziosis ankylostomiasis and other conditions (Courtesy Prof A Marchionini Ankara Turkey)

specific *malarial pigment* (hemozoin) is derived from the destroyed red cells. It contains iron but because of its firm grasp on the iron atom does not give the ordinary Berlin blue (Potassium ferrocyanide and FeCl) reaction It is taken up by the reticulo-endothelial system discoloring mainly the spleen liver and bone marrow and in extreme cases it may be found in the lumen of capillaries. The skin does not store the pigment however it may be found in blood vessels.

[144] Rosenthal, F and Löwenthal, K Addisonähnliche Form der Malaria Zentralbl f Haut- u Geschlechtskr 38 834 1931

Hemosiderin occurs besides the malaria pigment Skin pigmentations in malaria may also be caused by *melanin* [illegible] Chloasma like spots on the face are not rare These sometimes occur[illegible] as the peculiar mustache-shaped variety called chloasma periorale[illegible] which like many dermatoses of the lips leaves a thin white border

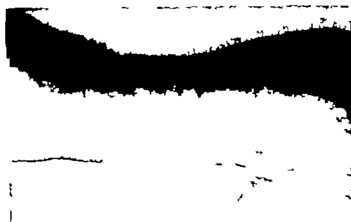


Fig. 68 — Malaria tropica morbilliform rash (Courtesy Prof A Marchionini, Ankara, Turkey)



Fig. 69 Gangrene in malaria tropica Courtesy Prof A Marchionini, Ankara, Turkey)

line between it and the vermilion area. Sometimes the pigmentations in malaria are pellagroid in distribution being found over the dorsa of the hands and the knuckles.

[illegible] Kaufmann E Die pathologischen Pigmentierungen der Haut in innerer Medizin Neurologie und Psychiatrie Handb d Haut Gk 4, 2 1011 1221 1933

[illegible] Marchionini A Malaria Cutaneous Changes Clinical Study Acta dermat venereol. 21: 290-319 40

[illegible] Pohr P V Durch Funktionsstörungen des weiblichen Genitalsystems hervorgerufene Hautkrankungen. Dermat Wchnschr 93: 293, 1930

addisonism in intensity and distribution including oral manifestations. Racial pigmentation of the gums can be ruled out by the effect of specific treatment which however removes malarial pigment deposits but slowly. Many authors have suggested that the adrenal cortex plays a part in the formation of the cutaneous pigment in malaria and there is some pathological evidence to support the clinical facts. F Rosenthal and Löwenthal[144] found in such a case almost complete atrophy of the adrenals. Two types of pigment occur in the skin. The



Fig 67 — Malaria tropica chloasma periorale and butterfly-shaped pigmentation over the cheek. Similar pigmentations have been described in bilharziosis, ankylostomiasis and other conditions. (Courtesy Prof A Marchionini Ankara Turkey)

specific *malarial pigment* (hemozoin) is derived from the destroyed red cells. It contains iron but because of its firm grasp on the iron atom does not give the ordinary Berlin blue (Potassium ferrocyanide and $FeCl_3$) reaction. It is taken up by the reticulo-endothelial system discoloring mainly the spleen, liver and bone marrow and in extreme cases it may be found in the lumen of capillaries. The skin does not store the pigment; however, it may be found in blood vessels.

[144] Rosenthal F and Löwenthal K Addison infolge Malaria, Zentralbl f Haut-u Geschlechtskr 24 531 1931

relapses of chronic malaria in up to 30 per cent of their cases In malaria countries it seems good advice to look for the parasites in cases of chronic and unexplained urticaria or even to try quinine as a diagnostic test.

Petechiae, purpura, and other *hemorrhagic* symptoms have often been reported In some of these cases[illegible] it could be shown that the petechiae were caused by arterial or capillary *thrombi* and vascular wall infiltration. *Plasmodia* could be demonstrated in the lesions Circulatory disturbances of the hands and feet may cause painful sensations of heat, as well as other paresthesias.

Gangrene of circumscribed areas, with or without Raynaud like symptoms and sometimes necessitating amputation is on record in a considerable number of cases.[illegible] It is probably caused by endarteritis. In the course of chronic malaria occasional dermadromes may occur due to the severe anemia (for example coilonychia[illegible]) The resistance to secondary infections is decidedly lowered Leishmaniasis cutaneous diphtheria, and other secondary infections may take an unusual course. The most spectacular secondary infection is *noma*. A Eckstein[illegible] (in Turkey) found malaria in nineteen out of twenty two cases. The patients were mostly small boys. There is a striking parallel between the incidence of noma and the malaria mortality in seasonal as well as in regional respects.[illegible]

Noma (Cancrum Oris; Stomatitis Gangrenosa)

Noma is a rare disease in western civilization Eckstein[illegible] saw only one case in ten years of service at the Düsseldorf Children s Clinic, while he observed no less than forty cases during three years in the Children s Hospital at Ankara Turkey Similar experiences have been reported from China. Epidemics of noma *were observed in former years in European hospitals. Almost exclusively a disease* of childhood noma is predominantly a nonspecific complication of acute infectious diseases. Measles, typhoid[illegible] congenital syphilis[illegible] and particularly malaria[illegible] are known to create the conditions in which the peculiar gangrene of the cheek occurs. Agranulocytosis and acute leukemia are other predisposing diseases.[illegible] 71 Some cases without known preceding disease have occurred.

The clinical picture shows a gangrenous stomatitis, which sometimes in a fulminating manner breaks through the cheek and upper lip and destroys all tissues, including the bone and teeth which lie in its path. Then the well known horrible destruction of one cheek surrounding the nose results. The lesion is

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Bruner L and Fraenkel E Das Malariaexanthem im klinischen od pathologisch-anatom. Bilde Arch f Schiffs- Tropen-Hyg 25 [illegible] 1921

Dore S E Cutaneous Affections in Various Diseases Brit J Dermat 18 41 1906

Lee K Gangrene of Feet in Acute Lat[illegible] Pernicious Malaria, Arch ed at i d Soc Ital. di chir 41 1013-[illegible] 93

Eckstein, A [illegible]matitis Gangrenosa Am J Dis Child [illegible] 319-337 940.

Laber S J and Ross D E A Case of Cancrum Oris Following Typhoid Fever With Plastic Repair Canad M A J 25 [illegible] 1931

Baltzer W Noma, Basel, 1937 Dissertation

Seifert, E Zur Krankheitsauffassung der Noma und gleichartiger Formen des Gewebsbrandes, Zentralbl f Chir [illegible] [illegible]-1863 [illegible]

Hicken, F Infectious Gangrene of the Skin Due to Bacterial [illegible], Arch. Surg 31 [illegible], 1935

decidedly unilateral causes little or no pain and temperature and even appetite are much closer to normal than one would expect a surprising observation which can also be made in the final stages of destructive oral cancers.

There is no strong leukocytic reaction[466] Only in the late stages does general toxemia develop The *post mortem examination reveals necrotic and degene* rative liver and spleen changes The mortality as based on 175 cases from the literature is 95 per cent. Eckstein[466] after switching from neoarsphenamine which proved disappointing to antigangrene serum in large doses locally intra muscularly and intravenously had more than 50 per cent recoveries in twenty one cases

Although there is no complete agreement about the cause it is assumed by most authors that Plaut Vincent s symbiosis of fusiform bacilli and spirillae plays an important part These microorganisms have frequently though not always[471] been found in the lesion and in the surrounding apparently normal tissues[466]

Amebiasis Cutis

Ulcerations of the skin caused by *Endamoeba histolytica* occur in amebiasis either in connection with an operative abdominal wound or around the anus or without direct connection with the infected viscera for example on the glans penis. The amebic ulcers[472] are rapidly spreading lesions. Varying activity in different portions of the margin causes an irregular jagged outline The edge is undermined purulent and surrounded by a red halo The floor is covered with indolent granulations and pus The skin lesions respond to emetine.

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[471] Friedmann J Ueber Noma der Wange Schweiz med W'nschr 1920 I 261 263

[472] Engman, M F J and Meleney H E Amebiasis Cutis (Endamoeba histolytica) Arch Dermat. & Syph 24 1 23 1931

CHAPTER VII

SYSTEMIC INFECTIONS

Rickettsial Diseases

Rickettsial diseases of man and many animals are caused by gramnegative coccoid or bacillary intracellular microorganisms which are usually borne by arthropods especially lice and ticks and which need tissue-containing media for successful culture. With the exception of the rickettsiae of the otherwise different Q fever they are not filtrable.[373] The serum of patients with rickettsial diseases agglutinates specifically certain strains of *Bacillus proteus* (Weil Felix reaction) The clinical appearance of the rickettsioses of the typhus group is best illustrated by its most important representative typhus itself from which the others differ but little.

TYPHUS FEVER

Typhus fever (typhus exanthematicus) is a severe endemic and epidemic disease the importance of which for the human race equals that of plague and cholera.[374] It has accompanied most of the wars and famines and other upheavels of history Its victims in Ireland during the early decades of the nine teenth century numbered millions. The epidemic form is possibly with a few exceptions spread by body lice. After an incubation period of thirteen to four teen days, the patient *suddenly develops fever chills severe headaches* and prostration The fever is continuous, ending by rapid lysis after approximately two weeks. Temporary mental disturbances during the fever and insomnia are common The attack is followed by a long period of convalescence which may last two or three months The attack is characterized by a rash stupor low blood pressure tender and enlarged spleen (denied by Gordon[375]) and various gastrointestinal and renal symptoms The loss of weight is very marked.[76] The blood show a shift to the left and thrombocytopenia which may reach 100 000 during the fifth to eleventh days.[77] The mortality rates vary widely Children and groups who have been exposed for a long time to infestation with lice are often only mildly ill In people beyond 50 years of age in the under nourished and n newcomers from disease-free countries who are not accustomed to body lice for example physicians and nurses the disease is apt to take a more severe course with mortality rates higher than 50 per cent.

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[373] Dyer R E The Rickettsial Diseases, J A M A 124 1165 1944

[374] Zinsser H Rats Lice and History New York 1934, Little Brown & Company

[375] Gordon D M Brill Disease J Michigan M Soc 39: 633-638 1940

[376] Virus and Rickettsial Diseases Harvard University Press, Cambridge M ss., 1940, article by J E Gordon, pp 829-871

[377] Schittenhelm A Das Fleckfieber Handb d inn. Medizin I 843-878 1925.

The gross pathology is unrevealing but the severity of the systemic infection is shown by typical widespread microscopic vascular lesions in the central nervous system the heart and especially the skin



Fig 75 Typhus lesion on the second day of exanthem Swelling of the endothelial cells and well defined perivascular cellular reaction (Courtesy Woodward, Th E and Bland, F F J A M A)

The infection conveys lasting immunity

The diagnosis is based on the clinical picture the epidemiologic conditions and the Weil Felix reaction Sometimes complement fixation tests and biopsy of a skin lesion are useful

Dermadromes.—The importance of the rash is reflected in the various names of the disease such as spotted fever typhus exanthematicus Fleckfieber fièvre exanthématique Murchison (after Curschmann [5]) collected nineteen different terms referring to the rash

In the first two days of the fever an *initial exanthem* consisting of a few ½ mm wide petechial papules on the trunk can sometimes be observed [176] The initial exanthem may occasionally be morbilliform or urticarial [177]

[5] Curschmann H Das Fleckfieber Nothnagel Spezielle Pathologie und Therapie Vol III Wien, 1900 Alfred Hölder

[177] Lipschütz B Die Klinik des Fleckfieberexanthems Arch f Dermat u Syph 126 414-437 1919

The main rash appears most often on the fourth to sixth day of the fever rarely as early as the second or as late as the ninth day [illegible] The eruption is often preceded by a characteristic drop in temperature In the early stages before it becomes plainly visible the rash can be demonstrated by a warm bath or a tourniquet.[illegible] The most comprehensive dermatological evaluation of the rash has been given by Lipschutz.[illegible] This article contains excellent illustrations.

The rash appears continuously and not in a series of crops so that the definite number of spots is reached within one or two days.[illegible] The eruption begins on the upper abdomen and chest then in rapid succession spreads to the back and to the extremities. The armpits and the inner surfaces of the upper arms are the places to look first for spots.[illegible] The fully developed rash may be extremely copious with the greatest density on the trunk From the trunk to the acra and to the face the density decreases on the whole with some accentuation on the dorsa pedum which is in contrast to the scarcity of lesions on the thighs and lower legs. Eruption on the palms and soles is not the rule. The exanthem starts with pale, ill-defined pinhead to lentil-sized hardly palpable often irregular maculae which as soon as they have reached a few millimeters in size no longer fade completely under glass pressure Confluence of neighboring lesions into irregular and slightly raised spots occurs. The color is not bright red but has an increasingly brownish tinge This indicates the *hemorrhagic component* which manifests itself in more or less numerous petechiae within and between the spots The purpuric phenomena are a measure of the severity of the infection [77] Purpuric lesions are often found in the folds and on the back. In the mature stage which is reached around the twelfth day the color is decidedly purplish and a delicately bluish marbled vascular pattern may be seen between the lesions which is easier to recognize from a short distance in moderately bright light. The old physicians called this subcuticular mottling or mulberry rash (Buchanan and W Jenner after Bäumler and Aschoff[illegible]) After the twelfth day the exanthem fades leaving yellowish brown pigmentation which may persist for a while A slight branny desquamation which can be provoked by gentle rubbing takes place during and some days after the fading [illegible]

In up to 20 per cent of the cases varying with the epidemics no exanthem could be observed A macular erythema is occasionally seen on the buccal mucosa It precedes the exanthem Initial conjunctivitis is common Herpes is rare The nails often register the severe disease by a white transverse line (Botkin and Pletnew after Schittenheim [77]) Pletnew [illegible] saw longitudinal *fluted lines*

The *micropathology* of the lesions has been studied by E. Fraenkel[illegible] and Bäumler and Aschoff [77] There are foci of hyaline degeneration necrosis and

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[illegible] Pletnew D Flecktyphus Moskauer Epidemie 1917 1920, Ztschr f. klin Med [illegible] 1922

[illegible] [illegible] Klinische und [illegible] Beobachtungen bei Fleckfieber Veröffentl. a. d. Geb. d. Medizinalverw [illegible]

[illegible] Dyer R E Typhus [illegible] The North America [illegible] 1943.

[illegible] Bäumler C and Aschoff L Fleckfieber Med Klin [illegible] 1918.

[illegible] Delamare [illegible] Note sur la desquamation furfuracée dans le typhus exanthématique Bull. Acad de méd [illegible]

[illegible] Fraenkel E Zur pathologischen Anatomie des Fleckfiebers, München med. Wchnschr [illegible] 1921

endothelial proliferation in the intima of the small arteries and precapillaries. These lesions form protruding intravascular buds and may give rise to small thrombi In the endothelial cells rickettsias have been found in small numbers [146] Furthermore there is a perivascular infiltration of lymphocytes plasma cells and epithelioid cells which resemble adventitial histiocytes These changes are found in the papillary vessels of the skin and especially throughout the brain and heart

No specific treatment is known A prophylactic vaccine is available

A mild variety of typhus known as Brill's[147] disease endemic or murine typhus with a mortality rate of less than 4 per cent is endemic in the east and southeast of the United States and in many ocean harbors. The disease is harbored by rats and transmitted by rat fleas and rat lice [148] The exanthem was seen in 64 per cent of 115 cases [148] appearing about the fifth day starting on the trunk and spreading centrifugally rarely reaching the face and palms. There often were only a few maculopapular lesions of 2 to 5 mm in diameter

Rocky Mountain Spotted Fever

Much more dangerous than endemic typhus is Rocky Mountain spotted fever Approximately 600 cases occur every year in the west and 200 additional cases in the remainder of the United States The average mortality is 12½ per cent This rickettsiosis is caused by Rickettsia rickettsii and transmitted by various ticks [149] The clinical picture resembles typhus closely A mottled initial rash has often been seen to appear with the fever thus preceding the exanthem[150] which breaks out between the second and sixth days of the illness It is rarely seen below the elbows and knees or on the face [71]

The rather copious rash is like the typhus eruption at first maculopapular and red especially in the evening later it is petechial and even frankly purpuric especially in severe cases The rash is followed by desquamation and pigmentation The individual lesion measures 2 to 4 mm in diameter [151] The rash may be extremely profuse[152] with hardly any normal skin left or it may be very sparse and even *completely absent It may appear in successive crops.*[153] Hemorrhagic factors may cause the usually discrete lesions to coalesce into purpuric areas which may involve the entire body Gangrene of the soft acra like the scrotum or the soft palate may occur [154, 150, 14] In abundant eruptions the skin is very tender The distribution is a little different from typhus in that the rash most often [14] appears first on the flexor surfaces of the wrists [14] and ankles

[146] Sikl H Rickettsias [illegible] bei hämorrhagischem Fleckfieber Časopis lékařů česk. [illegible] 6 -42 1931 Zbl 1 75

[147] Brill N E A Acute Infectious Disease of Unknown Origin Am J M Sc 139 [illegible] 1910

[148] Stuart B M and Pullen R L Endemic Murine Typhus Fever A [illegible] Med 23 520-536 1945

[149] Parker R R Rocky Mountain Spotted Fever J A M A 110 1185 1273 193[illegible]

[150] Anigstein L Spotted Fever Problem Clinics 2 [illegible]-913 1943

[151] Topping N H Rocky Mountain Spotted Fever M Clin North America 27 722 733 1943

[152] Floyd M L Rocky Mountain Spotted Fever J Iowa M Soc 27 [illegible] 1937

[153] Baker G E Rocky Mountain Spotted Fever [illegible] Year Study of Wyoming [illegible] Journal-Lancet 63 307 312 1 43

[154] Baker G F Rocky Mountain Spotted Fever Ann Int Med 17 [illegible] 1942

[155] *Ong R A and Raffetti J F Rocky Mountain Spotted Fever J Pediat 27 [illegible] 1945*



Fig. 73.—Rocky Mountain spotted fever. Severe case complicated by exfoliative dermatitis. Note embedded ticks in the skin of the neck and arms. (Courtesy Dr. G. R. Baker.)



Fig. [illegible]—Rocky Mountain spotted fever. [illegible] (Courtesy Dr. R. R. Parker, U. S. Public Health Service, Rocky Mountain Laboratory.)

spreading centripetally from there within two days[172] to the back, the arms the legs and the chest, and finally to the abdomen where it is least pronounced Palms soles and face are involved last[173] There is some relief of the muscular aches and pains after complete eruption

Fig. 75.

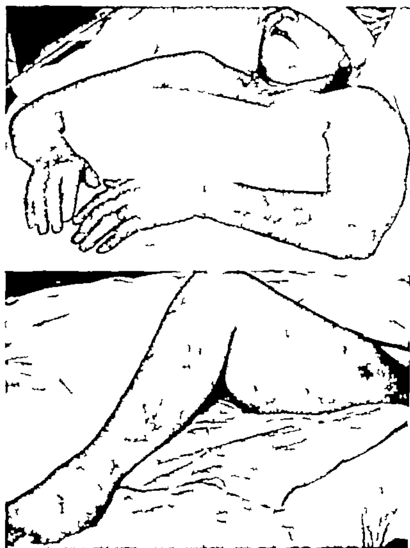


Fig 76

Fig 75 —Rocky Mountain spot ed fever Rash i petechial and of centrifugal distribution Acme Courtesy D G E Baker)

Fig. 76 —Rocky Mountain spot ed fever Not greater densi y toward the foot nd purpuric spots on the thigh Acme Courtesy Dr G E Baker)



Fig 77 —Rocky Mountain spotted fever Dense rash on the hands (Courtesy D G E Baker)

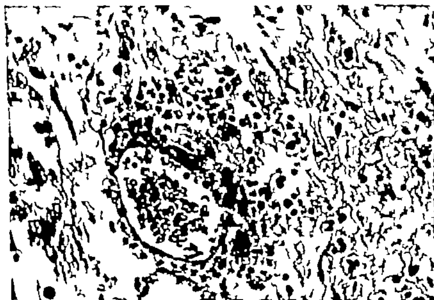


Fig 78 Rocky Mountain spotted fever skin lesions thirteenth day Cell Swelling of endothelial cells perivascular exudate From Dr R D Lillie Pathology of Rocky Mountain Spotted Fever U S Public Health Service

No specific treatment has become recognized except hyperimmune rabbit serum which is useful only during the first days. Early removal of the tick may prevent infection. A specific vaccine from egg yolk culture is of prophylactic value.[373]

Fièvre Boutonneuse, Marseilles Fever, or Fièvre Exanthématique Escarro-Nodulaire

Fièvre boutonneuse, Marseilles fever, or fièvre exanthématique escarro-nodulaire is a rickettsiosis of the Mediterranean areas. It is transmitted by a tick which feeds on dogs carrying the causative organism, Rickettsia conori. The course resembles mild typhus, the mortality rate being less than 3 per cent. The rash is more papular than in typhus[illegible] and later often purpuric. Cases without eruption occur.[17] The rash starts on the trunk, legs and arms and involves the face last. The palms and soles are commonly involved, the abdomen staying relatively free. At the onset, the tick bite is frequently visible as a lentil-sized shallow ulcer with a black necrotic center. This lesion is called tache noire.[illegible] It is of diagnostic importance but not always recognizable.

Tsutsugamushi Disease, Japanese River Fever, or Scrub Typhus

Tsutsugamushi disease, Japanese river fever or scrub typhus is a rickettsial *disease of the west Pacific area. It is endemic in flooded areas and along rivers.* The cause, Rickettsia orientalis, is transmitted by a mite which infests rodents, especially rats and a field vole.[illegible] According to Dyer,[illegible] the disease takes a typical typhus course of about seventeen days duration. The infecting bite causes a necrotic or scab-covered ulcer in about 75 per cent of the cases. The primary lesion is 2 to 10 mm in diameter with an indurated red areola and is accompanied by a smooth, tender, nonsuppurative lymphadenitis which only rarely extends beyond the portal area.[illegible] The initial eschar is of diagnostic value. The rash, which appears on the fourth day, is noticeable only in about one-half of the cases[illegible] and is often preceded by a dusky flush on the face and neck.[illegible] It resembles that of spotted fever, although Dyer[illegible] emphasizes the lack of hemorrhagic tendency. Characteristic eye ground changes and generalized peripheral lymphadenopathy are almost constant findings. The disease was known to have a fatality rate of 15 per cent, but in a recent series of sixty-four cases only 1.5 per cent of the patients died.[illegible] No specific therapy and no vaccine have been developed.

[illegible] Bolnet, P. J., and Dunan: Recherches nouvelles sur la fièvre exanthématique du littoral méditerranéen. Bull. Acad. de méd. Paris 100: 919-960, 1928.

[illegible] Raybaud, A.: Tache noire et fièvre boutonneuse. Bull. Soc. path. exot. 30: 625-627, 1937.

[illegible] Blake, F. G., Maxcy, K. F., Sadusk, J. F., Jr., Kohls, G. M., and Bell, E. J.: Tsutsugamushi Disease (Scrub Typhus, Mite-Borne Typhus) in New Guinea. Epidemiology, Clinical Observations and Etiology. Am. J. Hyg. 41: 243, 1945.

[illegible] Ahlm, C. E., and Lipshutz, J.: Tsutsugamushi Fever in the Southwest Pacific Theater. J.A.M.A. 124: 1095-1100, 1944.

[illegible] Marchette, T. E., and Forrester, J. S.: Tsutsugamushi Disease. Am. J. M. Sc. 210: 28, 1945.

Trench Fever or Wolhynia Fever

Trench fever or Wolhynia fever a benign recurrent fever common among soldiers of World War I is caused by a rickettsia found in the epithelial cells of the stomach of the body louse.[illegible] The observations on the frequency of macular micropapular scarlatiniform or petechial rashes and of erythematous enanthems vary widely.[illegible]

Carrion's Disease (Bartonellosis) Verruga Peruviana

In 1885 Daniel Carrión a Peruvian medical student, inoculated himself with blood and tissue from a lesion of verruga peruviana an eruptive disease occurring in certain South American valleys mainly in Peru. He died five weeks later of *Oroya* fever a clinically very different syndrome. This experiment strongly suggested the etiological identity of the two diseases which after much controversy has become generally accepted The cause of both forms which may occur independently simultaneously or successively[illegible] is Bartonella bacilliformis a minute rod-shaped parasite of the red blood cells. Culture (Battistini after Fox[illegible]) and animal inoculation[illegible] have been successful.[illegible] The infection is transmitted by the sandfly *Phlebotomus verrucarum* the habitat of which corresponds to the few areas of endemic Carrión's disease Fifteen to forty days after the infection the patient comes down with irregular fever malaise and anemia. If the disease takes the course of Oroya fever which has a mortality of 40 per cent the onset is sudden and the fever is at first continuous later remittant. The main feature is an acute severe anemia with a blood picture which resembles that of pernicious anemia The red count may fall as low as 500 000 In addition there is a leukocytosis of about 20 000 Fox[illegible] remarks that there is probably no condition except hemorrhage which can cause severe anemia so quickly The erythrocytes contain bartonellas in great numbers Skin lesions are scanty They are more numerous in the benign form called *verruga peruviana* which has the same incubation period but in which the fever and anemia are less severe

The Spanish word verruga is used for all types of cutaneous excrescences and it should not be taken as a synonym for the dermatological term verruca The characteristic lesions of the disease are nodules or tuberous masses which vary from pinhead to apple size and from a few usually large lesions to innumerable small efflorescences One therefore speaks of miliary and nodular forms, although there are many transitions. The rash comes on in crops and is itchy especially when it heals. The duration of the cutaneous form is variable on

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[illegible] Jungmann, P Das wolhynische Fieber Berlin 1919 Julius Springer

[illegible] Schittenhelm A Wolhynisches Fieber oder Fünftagefieber Handb d inn Medizin, Vol I Berlin 1925 Julius Springer

[illegible] Mera B Present Status of Human Bartonellosis, Bol Ofic san panam [illegible] 301-309 1943 Abst Trop Dis Bull 40: 904 1943

[illegible] Fox H Verruga Peruana—Personal Experience in Peru, J A M A 104 [illegible]-901 1935

[illegible] Jadassohn, J and Seiffert Ueber einen Fall von Verruga peruviana Uebertragung auf Affen Ztschr f Hyg Infectionskrankh 66: 247 1910

[illegible] Da Rocha Lima H Verruga peruviana oder Carrionsche Krankheit (Oroyafieber) Handb d H [illegible] Gk [illegible] 218-212 1932

the average from four to six months (Odriozola[447]) The miliary verrugas appear quite symmetrically on the extensor surfaces of the limbs on the ulnar aspects of the hands and forearms,[447] and on the face The body the palms and soles and the genitalia usually remain free.[444] The individual lesion starts as a flat red hemorrhagic papule. There are subcutaneous and cutaneous lesions the depth explaining the variations in color The nodule grows so that at first a sessile and later a pedunculated bluish-red conical or hemispherical tumor on a base of ringlike pigmented folds results. The lesions are firm at first but soften later Small lesions look like senile hemangiomas.[444] The verrugas bleed easily If the verruga is at its height the surface is glossy a little moist and the color cherry red much like a fresh hemangioma or granuloma telangiectaticum. The verruga has a marked spontaneous healing tendency It may shrink or drop by atrophy of the base Bleeding is common and secondary infection occurs. Lesions in the mouth the nose and the conjunctivae have often been observed They have been found in the entire length of the gastrointestinal tract and on the serous membranes. These lesions may cause serious hemorrhages [447]

Very large intracutaneous and subcutaneous sarcoid infiltrations of irregular shape may develop probably by coalescence of nodules. Large ulcerated granulomas are called mulas because the Peruvians believe that these big forms stem from infected mules. Infantile cases are usually mild

The histological picture shows a sharply bordered vascular granuloma which consists mainly of endothelial cells (verruga cells) and inflammatory infiltration. There are many variations some suggesting sarcoma angioma or myxoma.[444]

Da Rocha Lima[448] and other authors found in the protoplasm of the verruga cells inclusion bodies which were considered to be an adaptation of the bartonellas to intracellular life

The diagnosis rests on the unique dermatological aspect the history of a stay in a verruga area the fever and blood picture agglutination [449] and finally on the biopsy Leprosy and yaws must be ruled out.

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[448]Odriozola, E La maladie de Carrion ou la Verruga Péruvienne, Paris, 1898, Carré & Naud.
[449]Howe C Carrion Disease Arch. Int Med 72: 147 1943

CHAPTER VIII

SYSTEMIC INFECTIONS

Mycoses

Fungus infections are among the most common skin diseases but systemic mycotic infections are rare if one does not count the trichophytids

COCCIDIOIDOMYCOSIS

The name coccidioidomycosis is preferable to coccidioidosis a term which may easily be confused with the protozoonosis, coccidiosis. The disease is endemic in dry dusty areas of some western states,[459] especially the San Joaquin Valley in Southern California [460, 461] where from December 1937 to May 1939 432 acute infections of San Joaquin Fever were registered There is a peak of incidence in the fall. It is to the great merit of Dickson[460] to have shown that the acute respiratory infection known as San Joaquin Valley fever is the primary stage of coccidioidomycosis. The danger of such an endemic focus is illustrated by the fact that during recent military maneuvers in one of the endemic areas probably far more than the known seventy five cases occurred among several thousand soldiers.[462]

The cause is the fungus *Coccidioides immitis* which has a saprophytic hyphae phase and parasitic spherules or cysts which are double contoured refractile bodies which break up into radially arranged segments (endospores) In the infected person or animal these spores develop new spherules The infection is mainly air-borne and but rarely occurs through the skin. The acute disease does not seem to be contagious from man to man as shown by the failure to infect even a bedfellow

The air borne parasite causes a *primary lung infection* which probably often remains asymptomatic, but may manifest itself by severe chest pain irritating cough severe headache prostration and fever The whole syndrome resembles influenza or pneumonia.[463] In rare instances a primary lesion is found in the skin[464] A transient macular initial rash has been observed in some patients.

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[459] Smith, C E Epidemiology of Coccidioidomycosis With Erythema Nodosum, Am. J Pub. Health 30: 600-611 1940

[460] Dickson, E O Primary Coccidioidomycosis the Initial Acute Infection Which Results in Coccidioidal Granuloma Am. Rev. Tuberc 38 711 722 1938

[461] Smith, C E Coccidioidomycosis M Clin North America, 27 790-807 1943.

[462] Goldstein, D M and Louie S Primary Pulmonary Coccidioidomycosis, War Med. 4 299-317 1943

[463] Winn, W A and Johnson, G H Primary Coccidioidomycosis—Roentgenographic Study of Forty Cases, Ann Int Med 17: 407-422, 1942.

[464] Kessel, J F Coccidioidomycosis, Am J Trop. Med. 21: 447-453 1941

Fig 79 —Ery hema no losum lik rash in systemic coccidioidomycosis (San Joaquin fever) (Courtesy Dr C E Smith)



Fig 80 — Coccidioidomycosis scrofuloderma-like lesions about the neck Courtesy Dr H P Jacobson

Within the first three weeks of the acute respiratory phase erythema nodosum of typical distribution along the shins about the knees and on the lateral surfaces of the thighs, or erythema multiforme on the arms and occasionally on the face may break out. Goldstein and Louie[61] found an incidence of 25 per cent among infected soldiers all of whom probably were newcomers in the area but other percentages are much lower about 4 per cent.[60] Occasionally a morbilliform eruption has been noticed [61,62,63,64] Severe arthritic pains, sometimes with swelling of the joints,[64] have given rise to the term desert rheumatism. Conjunctivitis is sometimes a feature of this stage Eosinophilia is a frequent finding Smith[62] stresses the appearance of erythema nodosum at the time the coccidioidin test becomes positive.

The prognosis of the primary acute febrile phase is good the mortality being less than 1 per cent After recovering from an attack of San Joaquin fever the patient usually remains in good health without further attacks. The coccidioidin test remains positive for a long time

The diagnosis of primary coccidioidomycosis is hardly made from the clinical picture alone although tuberculosis-like X ray changes in the lungs[63] with negative bacillary and allergic findings may suggest it. The history of having lived in an endemic area the finding of spherules in the sputum and a positive coccidioidin skin test secure the diagnosis. The cutaneous reaction becomes positive two to seventeen days after the onset of symptoms. In about 1 out of 1000 cases a progressive secondary granulomatous develops which is fatal in more than 50 per cent and may predominantly involve the respiratory tract the bones the central nervous system and least often the skin. Coexistence of lung foci in cases which clinically seemed to be restricted to the skin has been demonstrated at post mortem [65] Several clinical varieties of a severe dermatosis have been described. Jacobson[66] classifies the lesions into those of cutaneous subcutaneous and lymphadenitic origin The skin nodules which in their further development may invade the subcutis, are mainly found on the face, about the neck, and on the distal parts of the extremities. The nodules are painless, deep seated and pink to dusky red They occur in various sizes and shapes and finally ulcerate and exude a grayish yellow pus containing *Coccidioides immitis* From these dermic lesions, fungating papillomatous granulomas may arise creating a picture resembling mycosis fungoides. Widespread cutaneous lesions may heal with atrophic scars. Chronic sarcoid and lupus vulgaris-like pictures have been observed [67]

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[60] Willett, F M and Weiss, A Coccidioidomycosis in Southern California Report of New Endemic Area, With Review of 100 Cases, Ann I Med 23 349 1 5

[61] Goldstein, D M and M Donald J B Primary Pulmonary Coccidioidomycosis 75 Cases, J A.M.A 124 557-561 944

[62] Faber H K Smith, C E and Dickson E C Acute Coccidioidomycosis With Erythema Nodosum in Children (San Joaquin Fever J Pediat 15 163-171 939

[63] Dickson, E C Coccidioides Infection, Ann Int Med 10 029 1937

[64] Rosenberg, E F Dockert M B and Meyerding, H W Coccidioidal Arthri is Unaffected by Sulfanilamide and Roentgentherapy Arch I Med 60 228-280 1 12

[65] Epstein, E Prognostic Significance of Cutaneous Lesions in Coccidioidal Granuloma, Arch, Dermat. & Syph 38 7?9- 85 193

[66] Jacobson, H P Immunotherapy for Coccidioidal Granuloma, Arch Dermat & Syph 40 821-840 1939

[67] Zeisler E P Chronic Coccidioidal Dermatitis, Arch. Derma & Syph 25 63-71 1932



Fig. 81

Fig. 82.

Fig. 81.—Coccidioidal dermatitis. Verrucous papules. (From Zeisler, E. P.: Arch. Dermat., 1932.)

Fig. 82.—Chronic coccidioidal dermatitis, later stages resembling blastomycosis. (From Zeisler, E. P.: Arch. Dermat., 1932.)



Fig 83

Fig 84.

Fig 83.—Chronic coccidioidal dermatitis. Crusted, active lesions and annular pigmented scars (From Zeisler E P Arch. Dermat. 1932.)

Fig. 84.—Coccidioidomycosis. Granuloma with giant cell containing sporulating cyst with capsule ruptured at one end. (From Zeisler E. P Arch. Dermat., 1932.)

The appearance of acute miliary pedunculated or sessile dermic granulomas usually on the face is of ominous significance.[illegible] Their appearance is often preceded by symptoms of pulmonary or meningeal involvement Such patients *usually succumb to the coccidioidal infection in from six to twelve weeks after* the appearance of the eruption In some of these cases the fungus could be grown from the blood

The course of the subcutaneous and lymphadenitic lesions is more chronic and relatively more benign The subcutaneous granulomas are frequently the *first cutaneous manifestations* [illegible] *They start as soft frequently tender masses* anywhere on the body and may form large flaccid tumors cold abscesses and sinuses If the flaccid tumor or abscess is surrounded by an extensive inflammatory infiltrate a hard gummalike lesion results Finally just as in tuberculosis to which many clinical parallels exist specifically involved superficial lymphatic nodes may especially in the submaxillary region create scrophuloderma like lesions with abscesses sinuses and scars

The histopathology of the coccidioidal lesions is that of an inflammatory granuloma with marked tuberculoid tendencies. There is edema and a diffuse cellular infiltrate predominantly composed of lymphocytes epithelioid and giant cells of the Langhans type These giant cells harbour the coccidioidal *spheres which have been demonstrated in the process of rupturing and releasing* the spores [illegible]

The treatment is still unsatisfactory Jacobson [illegible] who has had wide experience *with coccidioidomycosis reviewed in 1939 the many methods of treat*ment Intravenous injections of a 1 per cent solution of antimony and potassium tartrate [illegible] intramuscular injection of colloidal copper oral administration of potassium iodide arsenic or combinations of these agents and roentgen therapy have not given convincing results Jacobson [illegible] now feels that immunizing therapy is superior to the chemotherapy known so far and has had 20 per cent good results (personal communication) The patients are in intervals of one to two weeks given intravenous injections of vaccine starting with 0 05 c c and in*creasing by 0 05 c c each time A course consists of twelve injections* Between the courses is a rest period of six to eight weeks [illegible]

Torulosis

Only a few cases of systemic infection with the yeastlike fungus *Torula histolytica (Debaryomyces neoformans)* are known Tuberculosis resembling granulomas in the brain the lungs the gastrointestinal tract and other organs is the outstanding feature of the disease The comprehensive monograph of

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[illegible] E[illegible] N and Hall H A Coccidioidal Granuloma—50 Cases J A M A 93 1831 1929

[illegible] C[illegible] W H and Jacob F M Granuloma Coccidioides, Arch Dermat & Syph 16 309 1927

[illegible] [illegible] B A and Kimura F Skin Test for Coccidioidal Infection J Infect Dis 66 312 317 1940

Stoddard and Cutler[illegible] emphasized the *lack of skin manifestations* Since then a few cases with dermadromes have been reported [illegible]

Acneiform pustules, granulomatous ulcers and deep-seated abscesses nodules or plaques[illegible] varying from almond to hand size without ulcerative tendency have been observed The histopathologic characteristics of cutaneous torulosis include tuberculoid granulomas with caseation and enormous numbers of giant cells containing the double-contoured oblong or spheroid refractile organisms. There exists a close similarity between torulosis and coccidioidomycosis.[illegible]

Blastomycosis

H Montgomery[illegible] complains about the loose use of the term blastomycosis. He suggests that the word should be used only for the disease described by Gilchrist[illegible] in 1896 and not for all infections caused by yeastlike organisms.



Fig. 33 — Blastomycosis Primary lesion of neck resembling tuberculosis verrucosa

The American blastomycosis is caused by the yeastlike fungus *zymonema dermatitidis* which can be demonstrated in the pus or in the tissues as a refractile double contoured budding ound organism often appearing in unequal pairs.

Stoddard J L and Cutler E C Torula Infection in Man Monograph 6, New York, 1916, Rockefeller Institut for Medical Research

Urbach, E nd Zach F Generalisiert Torulose europäische Blastomykose) Arch. f. Dermat. u. Syph. 162: 401-12 1930

Rappaport, B Z and Kaplan B Generalized Torula Mycosis, Arch. Path 1 720, 1926,

Weidman, F D Cutaneous Torulosis South M J 26 851-863 1933,

Wile U J Cutaneous Torulosis Arch Dermat & Syph. 31 58-66 1935,

Montgomery H A steaic Blastomycosis, M Clin North America 14 651-662, 1930

Gilchrist T C Blastomycetic Dermatitis Johns Hopkins Hosp. Rep 1: 269, 1896

PLATE I

1. Acute septicemia. Bullous rash with hemorrhagic component. Fatal outcome.
2. Acute septicemia. Purpuric bullous rash.
3. Lupus vulgaris planum. Note brownish spots under glass pressure.
4. Tubercular ulcer of the tongue in pulmonary tuberculosis. (Case of Dr. J. Goodman.)
5. Systemic blastomycosis. Progressive skin lesion.
6. Systemic blastomycosis. Progressive and stable lesions.

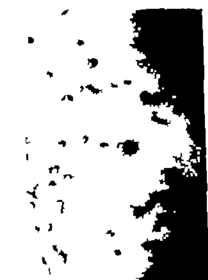







PLATE 1

Fig 66.—Blastomycosis. Leg lesion. Note bulging edge with small abscesses. In the pus of these abscesses one is likely to find the yeasts



Fig 67 —Blastomycosis Small skin lesion in systemic infection

The organism grows well on the usual fungus media where it develops mycelia which are not found in the lesions.

Blastomycosis may *occur as a primary skin infection and in the majority* of the cases it remains a dermatosis. A fraction of the skin cases may become systemic and involve other organs setting up internal foci which may metastasize and thus secondarily involve the skin [illegible] The widely scattered subcutaneous rather indolent nodules may develop slowly into cold abscesses which may reach large size The even and symmetric distribution of nodules and abscesses and their frequent involvement of the covered parts in contrast to the ectogenous lesions which favor the face arms and hands, indicate their hematogenous pathogenesis. The abscesses may form ulcers and sinuses from which typical blastomycotic skin lesions may arise



Fig. 43.—Blastomycosis. Gumma-like [illegible] lesion.

The primary skin lesion of blastomycosis is a papulopustule which slowly grows peripherally Within a few months it forms[illegible] a coin-shaped thick, firm elevated patch the surface of which is papillary or verrucous and often fissured or lobulated The center becomes depressed as soon as the lesion has reached the size of about a half dollar The most characteristic feature is the steeply *raised succulent red border in which many pin point* to pinhead sized abscesses are contained. By means of pressure and a magnifying glass they can easily be made visible The small quantity of pus which can be expressed from these tiny abscesses is the best material for microscopic study and culture These lesions may by growth and coalescence attain large size and even cover entire regions The center of such large lesions is often scarred but there are active foci scattered throughout the scar tissue in varying density The active foci in old lesions are often crusty oozing with serum and pus and apt to bleed on the slightest touch The destructive power of such large blastomycotic granulomas

[illegible] Ormsby, O [illegible] and Montgomery, H Diseases of the Skin Philadelphia, 1943 Lea & Febiger

is great. Prominent soft parts for example the scrotum [93] the alae nasi and the lids may suffer great damage. The polycyclic border of old lesions remains more or less papillary often cordlike The scarring does not always keep pace with the extension of the lesions so that large areas may remain thickly covered with red beds of vegetating masses. In other cases the peripherally progressing border leaves in its wake a smooth red ulcerative area almost devoid of any healing tendency



Fig [illegible] Unusually severe systemic blastomycosis This type of blastomycotic lesion resembles tuberculosis cutis verrucosa This case healed after three months of treatment [illegible] iodine and x-ray (From Bush J D Arch Derm [illegible])

In 50 per cent of th systemic cases th first symptoms are referable to the respiratory tract. The picture may resemble that of a cold or of an attack of influenza In 4 per cent the primary lesion followed an injury in 19 per cent a skin lesion was noted first and in 23 per cent the earliest lesion was a subcutaneous nodule or abscess often on unexposed parts.[94] Besides a great variety

[94] Martin D [illegible] and Smith D T Blastomycosis Review of Literature, Am. Rev Tuberc 39 [illegible]-304, [illegible]-518, 1939

of occasional organic involvements the bones mostly the vetebrae and joints, become infected in about 50 per cent of the systemic cases.

The histopathology reveals a granuloma with varying mixtures of leukocytes lymphocytes plasma cells and Langhans type giant cells which often contain some fungus elements Tubercle formation is not marked.

Enormous acanthosis and miliary abscesses throughout the hypertrophic rete as well as the corium are characteristic features.

The reservoir of the infecting fungus is probably on certain plants. Infection from man to man occurs only under extraordinary circumstances. The only such case known is that of a physician who injured himself at the necropsy of a case of systemic blastomycosis (Evans after Martin and Smith[94])

The age incidence has its peak between 20 and 40 years. Men are nine times as often infected as are women. The disease is far more common among the poorer classes.[94]

The prognosis of the systemic cases is almost invariably fatal The localized primary skin infection may take a chronic course but it will finally heal unless it becomes systemic, which is unusual

Clinical diagnosis from the skin lesions is often possible Other mycoses tuberculosis verrucosa syphilis and fungating granulomas must be ruled out The detection of the organism in the pus of small abscesses microscopically or by culture will usually confirm the clinical diagnosis For the microscopic examination the material is covered with a drop of 40 per cent KOH and examined in minimal light after at least ten minutes. A vaccine from heat killed fungi[94] is used in the diagnosis and treatment

Treatment.—Excision of small lesions may occasionally arrest the disease Irritating substances such as caustics often make the condition worse Potassium iodide in huge doses up to 25 Gm. daily [94,435] has often healed and often failed but it is nevertheless still the method of choice Combination with X ray therapy and vaccine may be judiciously used in combination with potassium iodide which loses its effect after prolonged administration Martin and Smith caution against the indiscriminate use of potassium iodide in hypersensitive cases. These cases should be desensitized by a series of vaccine injections.

Bosh, J D Blastomycosis, Arch Dermat. & Syph, 43: 488-490, 1941

Chapter IX

HELMINTHIC DISEASES

Trichinosis

It is now well established that trichinosis is a common human infection in the United States. A great number of post mortem diaphragm examinations conducted in various parts of the country[434-436] have shown that 12 to 18 per cent of the cadavers harbor trichinae. The infection stems largely from inadequately cooked pork, rarely from the meat of bears, wild boars, and some other large animals. A main source of infection of the swine is the practice of feeding them uncooked scraps of pork, while trichinous rats play a minor role.[437] On ingestion of trichinous meat the dormant and encysted worms are freed by the gastric juice. They propagate in the small intestine after one week. The young worms which are smaller than a red blood cell, are carried by the circulation to the muscles. Here they grow and encapsulate and may live for as many as thirty years.

The clinical picture of human trichinosis depends on such factors as massive infection or small size of the patient, tissues invaded, general resistance, and concomitant pathological conditions.[437] Many cases pass symptomless or undiagnosed. The clinical course can be divided roughly into three stages (Davaine after Beeson[439]) but it must be emphasized that this clearly defined sequence is seldom observed in practice. There is an initial gastrointestinal phase, starting sometimes hours after the ingestion of trichinous meat. At the end of the first week, it is followed by a stage of dissemination marked by prostration, facial edema, fever, sweating, and pain in the muscles of respiration, mastication, and the eye. After six weeks the disease passes gradually into the stage of encystment of the worm in the muscles while the severe symptoms ease up and the fever subsides. Edema, muscular pains, and anemia may persist for a long time. The average mortality which was very high in some German epidemics of the nineteenth century is probably less than 5 per cent of the clinical cases in the United States.[438] Most deaths occur from the fourth to sixth week and are due to myocarditis or bronchopneumonia.[440] There are indications that existing infection protects against reinfection.[438]

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[434] Hall, M. C. and Collins, B. J.: Studies on Trichinosis, Pub. Health Rep. 52: 468-490, 1937.

[435] Hall, M. C.: Studies on Trichinosis, Pub. Health Rep. 52: 539-551, 1937; 53: 1472-1486, 1938.

[436] Kerr, K. B., Jacobs, L., and Cuvillier, E.: Trichinosis, Post-mortem Examination of 3,000 Diaphragms From Washington, D. C., and Five Eastern Seaboard Cities, Pub. Health Rep. 56: 836-855, 1941.

[437] Gould, S. E.: Trichinosis, Springfield, Ill., 1945, Charles C. Thomas, Publisher.

[438] Gould, S. E.: Method for Control of Trichinosis in the U. S. A., J.A.M.A. 129: 1251-1254, 1945.

[439] Beeson, P. B.: Trichinosis—Clinical Manifestations, Lancet 1941, 2: 67-69.

[440] Diener, O.: Trichinosis, Connecticut M. J. 4: 314-317, 1940.

[441] Wyrens, R. G., Tillisch, J. H., and Magath, T. B.: Trichinosis, J.A.M.A. 117: 426-433, 1941.

The blood changes are characteristic. There may be severe anemia and leukocytosis *Eosinophilia* is an almost invariable sign in the second stage. It may range from a few to 73 per cent[444] and is considered the most reliable diagnostic sign[445] However eosinophilia may be missed or disappear in severe cases.[444]

A *cutaneous immediate urticarial reaction with an allergen from digested* trichinous meat has been developed by Bachman.[446] Besides the immediate response which appears within thirty minutes a *delayed* reaction may occur after two days. This test is supposed to become positive in the third week of illness.[164,447,448] The reaction is about as reliable as the precipitin reaction which becomes positive in the fourth week[449] or as the complement fixation test.[450] Considering the frequency of trichinella infection a positive skin reaction is only valuable if supported by other evidence of recent infection or if it has turned positive while the disease has been observed[149] The test* may be negative in very severe cases.[164,451,452] In all tests group reactions against other common worm infections must be borne in mind[453] For example Fülleborn[454] mentions a case of a patient infected with echinococcus who gave a positive reaction to echinococcus antigen as well as to antigen from *Cysticercus tenuicollis* trichinella and strongyloides There is also a common antigen in ascaris and trichinella[149] and pinworm and trichinella.[149] Muscle biopsy (gastrocnemius) is rarely necessary The muscle specimen should be pressed between two glass slides and examined at low power as is done in the testing of meat Trichinae can occasionally be centrifuged from the stools the bile the arterial blood[455] or the cerebrospinal fluid[456]

Dermadromes —The scarcity of cutaneous lesions is in agreement with the rarity of the presence of trichinae in the skin of experimentally infected mice[456]

Edema of the eyelids is the most common and in fact the only dermadrome which is seen in the majority of the cases. It is an early important sign of mus-

*The allergen can be obtained from the National Institute of Health in Bethesda Md which also does the precipitin test on serum sent in for this purpose

[444] Murphy F D James, H D and Rastetter J W Trichinosis 89 Cases, Am J M Sc 199 338-338, 1940

[445] McNaught, J B Laboratory Procedures for the Diagnosis of Trichinosis, Am J Clin. Path Tech Sect 8 87-93 1944

[446] Bachman G W An Intradermal Reaction in Experimental Trichiniasis, J Prev Med 2t 513-523 1928

[447] McNaugh J B Diagnosis of Trichinosis, Am J Trop Med, 19 181 193, 1939.

[448] Hall, A A Trichiniasis Use of the Bachman Intradermal Skin Test Ann Int Med 10 1544-1550, 1937

[449] Kaufman, R E Trichiniasis Clinical Considerations, Ann Int Med. 13 1431 1460 1940.

[450] Gasse A Trichinosis Serodiagnosis With Complement Fixation München med Wchnschr 88 473-474 1941

[451] McNaught, J B Medical and Public Health Aspects of Trichinosis, Texas State J Med 38 233-235 1942

[452] McNaught, J B Beard R R and Myers, J D Diagnosis of Trichinosis by Skin and Precipitin Tests, Am J Clin Path 11 196-201 1941

[453] Jadassohn, W Die Immunbiologie der H Handb d H Ok 2 41 1932

[454] Fülleborn, F Diagnostische Cutanreaktion bei Helminthenkrankheiten, Klin Wchnschr 7 830, 1928

[455] Dammin, G J Trichinosis—Report of Case With Demonstration of Larva in Arterial Blood New England J Med 224 357-360 1941

[456] Mauss, E A and Otto G F Occurrence of Trichinella Spiralis Larvae in Tissues Other Than Skeletal Muscles, J Lab & Clin Med 27 1384-1387 1942

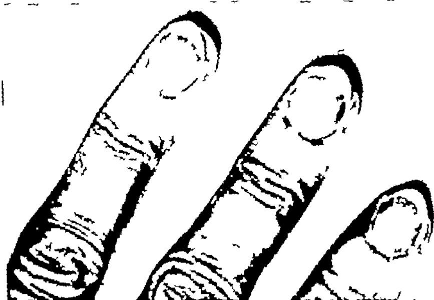


Fig. 90.—Splinter hemorrhages in trichinosis. (Courtesy McNaught, J. B.: Am. J. Trop. Med., [illegible].)

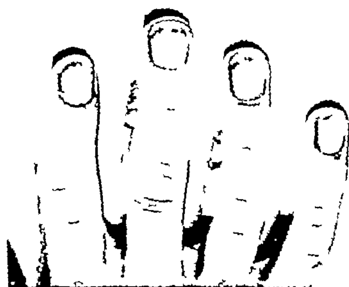


Fig. [illegible].—Trichinosis. Splinter hemorrhages arranged in cross lines indicating simultaneous genesis. (Courtesy Dr. [illegible].)

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[644]Murphy F D James H D and Rastetter J W Trichinosis [illegible] Cases, Am J M Sc 199 [illegible]-[illegible] 1940

[645]McNaugh J B Laboratory Procedures for the Diagnosis of Trichinosis Am J Clin Path Tech Sect 8 7-[illegible] 1944

[646]Bachman G W An Intradermal Reaction in Experimental Trichinosis J Prev Med 2 513-523 1928

[illegible]McNaught J B Diagnosis of Trichinosis Am J Trop Med [illegible] 181 [illegible], 1929

[illegible]Hall, A A Trichinosis Use of the Bachman Intradermal Skin Test, Ann Int Med 10 1514-1530 1937

[illegible]Kaufman R E Trichinosis Clinical Considerations Ann Int Med 13 1431 1440, 1940

[illegible]Gaase A Trichinosis Serodiagnosis With Complement Fixation München med Wchnschr 88 473-474 1941

[illegible]McNaugh J B Medical and Public Health Aspects of Trichinosis Texas State J Med 38 232-235 1942

[illegible]McNaugh J B Beard R R and Myers J D Diagnosis of Trichinosis by Skin and Precipitin Tests, Am J Clin Path 11 [illegible]-[illegible] 1941

[illegible]Jadassohn W Die Immunbiologie der Haut Handb d H [illegible] k 2 18 1933

[illegible]Fülleborn F Diagnostische [illegible] tanreaktion bei Helminthenkrankheiten Klin Wchnschr 7 [illegible] 1928

[illegible]Damrain J Trichinosis Report of Case With Demonstration of Larvae in Arterial Blood New England J Med 224 357 360 1941

[illegible]Haase E A and [illegible] F Occurrence of Trichinella Spiralis Larvae in Tissues Other Than Skeletal Muscles J Lab & Clin Med 32 [illegible] 357 [illegible]

Ancylostomiasis (Hookworm Disease)

Ancylostomiasis (Hookworm Disease) The hookworms[864] for medical purposes the genera ancylostoma and necator are duodenal human parasites whose larvae leave the bowel with the feces in great numbers. These larvae are about 0.5 mm. long They enter the body through the unbroken skin especially the thin skin of the instep area and are carried by the lymph and blood to the lungs from where they follow the bronchotracheal tree into the larynx pharynx, and finally the gastrointestinal canal (Looss after H Bruns[865]) to their living and breeding place the duodenum The hookworms are found chiefly in warmer climates. They have caused epidemics in warm countries among barefooted workers on rice, tea, mulberry and similar plantations and in colder climates among miners working in the warm and humid shafts.

The disease is common in the southern section of the United States and especially in Puerto Rico The infection causes a severe often fatal progressive anemia and involvement of many organs.

Dermadromes —When the larvae penetrate the skin of the feet they cause itching vesicular dermatitis and possibly secondary infection. However a controversial point is to what extent hookworm causes the ground itch of the south or mazamorra of Puerto Rico and Central America a common eczematous condition of the feet. Fülleborn[864] denies that the majority of the ground itch cases have anything to do with ancylostomiasis. It is claimed that *Necator americanus* is more likely to cause ground itch than *Ancylostoma duodenale*[866]

If the hookworm infection has become fully developed *pruritus* marked *dryness* of the skin and hair reduced perspiration on exertion and heat and *burning of the palms* are reported to be troublesome symptoms (Ashford and King after Fülleborn[864] The features are reported to become blurred and slightly puffy shift of pigment takes place[868] and persistent acne may occur A butterfly-shaped pigmentation over the bridge of the nose has at times been thought to be diagnostic of schistosomiasis but this is not true since such pigmentations occur also in other infections (bilharziosis) and probably also in various nonhelminthic conditions. The diagnostic value of minute black or brown spots on the side of the tongue or on the lips in patients with hookworm is doubtful[867-868]

Creeping eruption caused by the larvae of *ancylostoma braziliense* and other nematodes, is not always restricted to the skin[869-870] It may like other worm

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[864] Fülleborn F Haut und Helminthen Handb. d H. u. Gk 12, 1 706-800, 1932.

[865] Bruns, H Die Ankylostomiasis in der gemässigten Zone Handb d path. Mikroorg 6, 2 907-918, 1929

[866] Dörrmann, O Die Ankylostomiasis der Tropen und Subtropen, Handb d. path. Mikroorg. 6 2 919-994 1929

[867] Sutton, R L and Sutton R L J Diseases of the Skin, St Louis, 1939 The C V Mosby Co.

[868] Jeghers, H Pigmentation of the Skin, New England J Med. 231 88-100, 122-136, 181 189 1944

[869] Millspaugh, J A and Sompayrac L M Hookworm Infection, Creeping Eruption, Infestation With Ancylostoma Braziliense U S N M. Bull. 40 303-306, 1942.

[870] Kirby-Smith, J L Dove W E and White, G F Creeping Eruption, Arch. Dermat. & Syph. 13 137 173, 1926

infestations and some bacterial infections be accompanied by transient and migratory pulmonary infiltrations with few or no symptoms. This is known as *Loeffler's syndrome*.[471]

Ascariasis

Infestation with large roundworms has been held responsible for a number of dermatoses. It is certain that ascarides contain a highly sensitizing allergen which may explain cases of urticaria, angioneurotic edema, pruritus nari, epistaxis, and eczema. The same precaution as is used in the evaluation of allergic tests in other worm infections (see under trichinosis) must be used in the skin tests for ascarides.[446, 464, 471, 472] The possibility of anaphylactic shock with asthma and urticaria in repeated intracutaneous tests with ascaris antigens is emphasized by several authors.[473] Another difficulty is that at least in some areas, for example the southeastern parts of the Appalachian range,[448] the incidence of a sensitization to ascaris is so widespread among the population that the test loses its diagnostic value.[474] The pathogenesis of some skin lesions, for instance pruritus ani, eczema of the hands, itching of the nose, and bullous or acneiform eruptions,[475] *may be explained by local reactions to the worm allergen in ova* carried and inoculated by the hands. Several observers have expressed the thought that the itching and scratching of the nose in worm infestation, which is so common in the tropics, is an important cause of the first infection with leprosy.

Oxyuriasis

Similar conditions of allergy, combined with the mechanically caused itching produced by the migrating worm, exist in pinworm (*Enterobius* or *Oxyuris vermicularis*) infestation. The worms[476] live in the lower ileum and cecum but descend to the rectum for egg laying. From there they may at night reach the anus and occasionally distant skin areas. Scratching and inoculating of the crushed worms or eggs may cause local allergic reactions.[477] Neurodermatitis which responded to anthelmintic treatment and flared up on injection of oxyurus extract has been described.[478] Biting of the nails, sucking of the thumb and picking at the nose, often considered suggestive of worm infection, were *found no more frequently in infested persons than in control groups*.

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[471] Wright, D. O., and Gold, E. M.: Loeffler's Syndrome Associated With Creeping Eruption, J. A. M. A. 128: 1082-1083, 1945.

[472] Nagel, B.: Die Cutireaction bei Ascaris lumbricoides, Istanbul Seririyat ... 4: 75-78, 1937; Zbl. 58: 420.

[473] Schönfeld, W.: Ascariden-rakte ... Arch. f. Dermat. u. Syph. 175: 61-70, 1937.

[474] Diehl, F., and Schwoerer, P.: Allergie der menschlichen Haut gegen Ascaris lumbricoides, Arch. f. exper. Path. u. Pharmakol. 183: ... 736.

[475] Schütz, J.: Helminthen bei Hautkrankheiten und ihre Behandlung, Dermat. Wchnschr. 80: 807, 1925.

[476] Cram, E. B.: Oxyuriasis, Am. J. Dis. Child. 65: 46-49, 1943.

[477] Cieszyński, F. K.: Hautreaktionsversuche mit Helminthenextrakten bei Kindern, Monatschr. f. Kinderh. 39: 61-71, 1928.

[478] Schröpl, E.: Neurodermitis durch Oxyuren, Dermat. Wchnschr. 83: 1093-1097, 1930.

The *diagnosis* rests on the finding of worms or their ova. The latter are best collected with a few energetic strokes in a peripheral direction from the anus, with a cellophane (Scotch tape) tipped swab.[579] The cellophane is then examined on a slide moistened with water and covered with a cover slip. A skin test with enterobius antigen may be helpful.[579-580] Brady and Wright[581] were unable to find any typical cutaneous lesions in 200 controlled cases. In a series of tests, Brady and Wright[581] found that gentian violet given by mouth was superior to other methods. The dosage of the drug for adults was two 32 mg. tablets three times a day before meals, and for children 10 mg. a day for each year of their apparent, not actual, age, the total amount being divided into three doses.

Filariasis

Wuchereria (*Filaria*) *bancrofti* is a nematode of the warm climates. The adult worm, which is as thick as a strong hair and several centimeters long, lives in the human lymphatics and produces tremendous numbers of microfilariae which are about 0.3 mm. long and no thicker than a red blood cell. These microscopic worms live in the blood, appearing in great numbers at night in the peripheral blood and retreating at day into the visceral arteries. The microfilariae pass part of their development in various mosquito vectors, but they are brought back into man to complete their life cycle. According to Manson Bahr,[582] Fülleborn[583] and other authorities on tropical medicine, the microfilariae, in spite of their number, have no pathogenic properties, while in a certain proportion of instances the obstruction of lympatics caused by the *adult* worm causes *lymphedema, lymphatic varicosities* and *elephantiasis*. The monstrous enlargements of legs, mammae, scrotum and other parts are well known pictures of tropical pathology. The lymph stasis, inflammatory reaction, scarring and calcification caused by the adult worms may be permanent. The lesion is likely to become infected with hemolytic streptococci causing the repeated erysipelatoid attacks which are the more immediate cause of elephantiasis.[582-584] Other authors believe that elephantiasis may develop without acute attacks.[584] Grace[585] feels that there is no evidence that *Wuchereria* (*Filaria*) *bancrofti* plays any part in the production of the attacks of lymphangitis. Recent observations on military personnel in endemic areas[586] have shown that acute lymphangitis of arms or legs and acute funiculitis or epididymitis with little fever or general symptoms are the outstanding early clinical symptoms. Peculiar features are a centrifugal lymphangitis which may work down from the

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[579] Hall, M. C.: Studies on Oxyuriasis. I. Types of Anal Swabs and Scrapers, Am. J. Trop. Med. 17: [illegible], 1937.

[580] Tsuchiya, H. and Bauernfeind, T. C.: Intradermal Test as Aid in Diagnosis of Enterobiasis, J. Lab. & Clin. Med. 24: 627-631, 1939.

[581] Brady, F. J. and Wright, W. H.: Oxyuriasis, 200 Cases, Am. J. M. Sc. 198: 367-372, 1939.

[582] Low, G. C.: Pathology of Filariasis, J. Stat. Med. 39: 304-305, 1931.

[583] [illegible], S. L.: Filariasis and Elephantiasis, Nederl. tijdschr. v. geneesk. 76: 3773-3776, 1932; Abst. 43: 159.

[584] [illegible], L.: Clinical Studies of Filariasis, Geneesk. tijdschr. v. Nederl.-Indië 73: 647-[illegible], 1933.

[585] Grace, A. W.: Filariasis, Tropical Lymphangitis and Abscesses, J. A. M. A. 123: 405-406, 1943.

[586] Thompson, K. J., Rifkin, H. and Zarrow, M.: Early Filariasis in Young Soldiers, J. A. M. A. 129: 1074-1080, 1945.



Fig 92 —*Microfilaria of L loa in blood film (X1 700)* *Actual length 168 microns* *The only* successful preparations ere made from the blood taken from Calabar swelling on the forearm in the late afternoon. Giemsa stain. (From Guy W H Cohen, M and Jacob F M Arch. Dermat., 1943)



Fig 93 —Calabar swelling. From G y W H., Cohen, M and Jacob, F M. Arch. Dermat 1943.)

upper arm to the waist and lymph nodes in unusual sites for example the tip of the ileum the midarm and the region of the serratus and teres muscles. Centripetal lymphangitis occurs also In the chronic stages the skin manifestations are due mainly to the enormous lymphatic varicosities and enlarged lymph nodes which may cause dome-shaped pseudovesicles of the skin A positive *reaction to an intradermal injection of* 1:4000 *filaria antigen* is considered diagnostic.[486] Other worm infections do not respond to a dilution higher than 1:2000 *Filaria loa* an African species transmitted by a fly migrates in the connective tissue, often near or in the skin or beneath the bulbar conjunctiva producing the so-called *Calabar swelling* these lesions appear on the forearms or less commonly over the ankles or on the face They probably represent an allergic

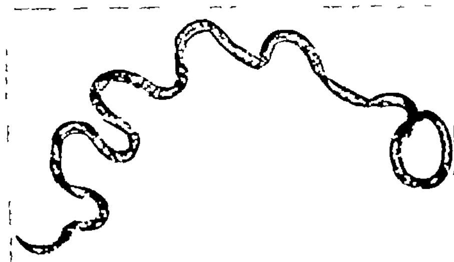


Fig 91 — Filaria of L. loa (X6) actual length 40 mm Adult worm removed from the conjunctiva of missionary returned from the Cameroons, Africa Note the ... structures and the twist at the caudal end (From Gay W H Cohen M., and Jacob, F M. Arch. Dermat. 1943)

reaction to the worm or its products The worm or calcified remnants of it have been demonstrated by roentgenogram[487] The swellings are usually rather painless but sometimes itchy They disappear after a few days or rarely after weeks,[488] only to recur somewhere else.[489] Scabies-like itching eruptions are known as filarial prurigo or gale filarienne[490] Besides the mentioned skin tests, complement fixation reactions in filariasis have been developed.[491-492] Eosinophilia may reach 24 per cent.[492]

[487] Greig E D W Filariasis, Cases of Calabar Swelling With Radiologic Observations, J Trop Med 43 19-21 1940.

[488] Gay W H Cohen, M and Jacob, F M Infection With Loa-Loa, Arch Dermat & Syph. 47 763-767 1943

[489] Stefanopoulo O Filarial Prurigo or Gale Filarienne in Case Due Loa Loa Trop Dis Bull. 401 482. 943

[490] Fairley N H Skin Test and Complement Fixation in Filariasis, Tr Roy Soc Trop Med. & Hyg 25 220-221 1932,

[491] Rodhain, J and Dubois, A Intradermal Reactions in Human Filariasis, T Roy Soc. Trop Med & Hyg 25 377-382, 1932

[492] Low G C Skin Conditions Found in Loa Loa Infections, J Trop. Med. 37 ...-...; 1934

An eosinophilic disease with migratory edematous swellings which has lately been observed in small epidemics in Palestine probably is related to Calabar swelling.[illegible]

Onchocerciasis

Onchocerca is a nematode which resembles filaria in many respects. The life cycle, which is not fully understood, is partly spent in flies of the genus Simulium. The adult worms and great numbers of microfilariae live in cystic tumors (onchocercomas) of the subcutis. The majority of the patients with onchocercomas present no demonstrable cutaneous manifestations. However, microfilariae have been found in great numbers in apparently unaffected skin[illegible] as well as in the blood. The onchocerca nodules are pea to almond-sized and occur most frequently over the skull, which they may perforate, along the costal arches and about the joints, where they may simulate juxta-articular nodes. There is an African type caused by *Onchocerca volvulus* and a Central American type caused by *Onchocerca caecutiens*. The latter is restricted to parts of Guatemala and Mexico. The American onchocerciasis is of importance because of the keratitis and iritis which accompany many cases and which may lead to blindness (onchophthalmia).[illegible] Acute febrile erysipelatoid swellings of the face and of the limbs, characterized by hardness and a greenish hue, and transitions into chronic edema occur among patients with onchocerca nodules (Robles after Fülleborn[illegible]). In both types of onchocerciasis the skin may become dry, itchy, infiltrated and coarsened (onchodermatitis). This pruriginous phase may look much like scabies[4] or neurodermatitis.[illegible] The microfilariae of *Onchocerca volvulus* can be found in the alterated skin. Itching seems to be caused by allergic phenomena rather than by the active moving of the worms, since heavily infected skin was found without associated pruritus.[illegible]

Dracunculiasis or Dracontiasis (Guinea Worm)

The guinea worm (*Dracunculus medinensis* or *Fuellebornius medinensis*, formerly called *Filaria medinensis*) is, in its larval stage, a parasite of some microscopic crustacea of the genus cyclops which infests man through drinking water or through direct entrance into the skin. After one year the adult fertilized female, which is one yard long and about as thick as a thread, appears under the skin, sometimes preceded by fever and urticaria.[illegible] A dome-shaped blister, later an ulcer, indicates its end. The lesion varies in diameter from 2 to 7 mm.[illegible] On

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[illegible] Lefko[illegible] and [illegible]: Clinical Picture of Eosinophilic Disease With Cutaneous Manifestations, [illegible] Harefuah 23: 122, 194[illegible].

[illegible] Goldman, L.: American Onchocerciasis, Arch. Dermat. & Syph. 137: 355-290, 19[illegible].

[illegible] Hoffmann, C. C., and Vargas, L.: Nuevas comunicaciones acerca de la onchocercosis de Chiapas, Rev. mex. de biol. 13: 137-147, 193[illegible]; Zbl. 41: 785.

[illegible] Fülleborn, F.: Ueber juckende Hauterscheinungen bei [illegible] deutschen Onchocerca-Trägern in Südamerika. Nebst einer Zusammenfassung über die [illegible] Onchocerciasis [illegible] Dermatosen und Versuche über den diagnostischen Wert der [illegible] Onchocerca-Antigen. Arch. f. Dermat. u. Syph. 164: 214-22[illegible], 1931.

[illegible] Anderson, C., and Lebucher, P.: Onchocercose Cutanée en Tunisie, Arch. Inst. Pasteur de Tunis 29: 103-112, 1940.

[illegible] Loewenthal, L. J. A.: Onchocerciasis: Cutaneous Changes, Ann. Trop. Med. 37: 147-148, 1943.

douching with cool water the worm will often protrude from a small hole and expell a fluid containing thousands of embryos.

The premonitory urticaria and pruritus and also asthma and diarrhea are probably caused by the same allergens in the excreta which cause the blister and ulcer The microfilariae do not have the toxic or allergenic effect of the adult worm[illegible] which if injured or dead sometimes causes severe reactions. The therapy consists in cautious and patient extraction of the entire adult worm which takes about two weeks This requires a certain technique which can be found in the textbooks on tropical diseases [illegible]

Cysticercosis

Normally the adult tapeworm (usually *Taenia solium*) is a parasite of the human ileum Its eggs must get into the stomach of the swine where the hatched embryos travel to the points of encapsulation Occasionally man is the intermediate host instead of the pig Then he will harbor the encapsulated larvae most often in the brain and the eye only in 6 per cent of the cases in the subcutaneous tissues. The subcutaneous or cutaneous cysticerci are cysts of from one to several centimeters in diameter They are round or oblong and are freely movable in the subcutaneous tissue The cysts are of elastic hardness and nontender numbering a few or several thousands. The inflammatory reaction is insignificant. If they are diagnosed they may help to explain other symptoms caused by cysticercosis of internal organs [illegible] The prognosis of cysticercosis of the skin per se is favorable. The cysts usually stay without change and sometimes disappear spontaneously The huge *echinococcus* cyst is the larva of a small tapeworm of the dog The disease is very rare in the United States. An intracutaneous test with liquid from the cysts (Casoni test) and a complement fixation test are reliable.

The larvae of some tropical cestodes (*Sparganum proliferum*) may cause small acne like cutaneous cysts besides severe involvement [illegible] of almost the entire system in some of the few studied cases.[illegible]

Bilharziasis

The adult worms of *Schistosoma hematobium* live in pairs in the portal system of man producing eggs which appear in the feces and in the urine. In water

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[illegible] Fairley N H and Liston W G Studies in the Pathology of Dracontiasis I. Indian J M Research 11 915-932 1924

[illegible] Fairley N H Studies in Dracontiasis VI Indian M Gaz. 59 430-435, 1921

[illegible] Takamatsu H Generalized Cysticercosis, Zentralbl f allg Path u. path. Anat. 72: 2-3, 1939.

[illegible] Tamamura I and Repeh E Ein Fall von Cysticercus bovis im Unterhautgewebe des Menschen Virchows Arch f path Anat 301 335-345, 1938

[illegible] Fick W Tierische Parasiten der Haut Handb d H u. Gk. 8, 1 467-614 1929.

[illegible] Brailsford, J F Unrecognized Cysticercosis, Lancet 1 127 129, 1942

[illegible] H C K Oo-Kek K and Frazier C N Subcutaneous Cysticercosis Cellulosae in Man. Five Cases Arch Derm & Syph 21 777 760 1930

[illegible] Stiles, C W and Taylor L The Larval Cestode (Sparganum [illegible]) of Man Which May Possibly Occur in Returning American Troops, Bull 35 Bureau of Animal Industry U S Dept Agriculture, Washington, [illegible]

they develop into larvae (cercariae) which are able to enter the human body through the skin

Bilharziasis is predominantly a urinary disease It is a public health problem of great importance in Egypt, Japan China, and other countries, especially where work in flooded rice fields brings about the exposure to infection with cercariae

Dermadromes.—The dermadromes are of little importance in comparison with the frequent and severe bladder involvement The skin in the neighborhood of the urinary fistulae may contain huge numbers of often calcified eggs. The irritation from urine pus and infestation may give rise to *papillomas* of the anal and genital region which occasionally become malignant. Sinderson[197] found in 20 per cent of the schistosomiasis (hematobium) cases that he observed in Iraq a sometimes reticulated well-defined butterfly-shaped *hyperpigmentation* over the bridge of the nose and the cheeks. He believes that it is caused by a photosensitization of the skin under the influence of the worms (see under ancylostomiasis)

The entering cercariae of schistosoma hardly cause[198] dermatitis while the cercariae of otherwise innocuous trematodes have been held responsible for many epidemics of *swimmers itch*

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[197] Sinderson, H C Anomaly of Pigmentation in Schistosomiasis, Tr Roy Soc Trop. Med 23 633-634 1930.

[198] Lutz, A and Lutz, G A Bilharziosis oder Schistosomuminfektionen, Handb d path. Mikroorg 6, 2 873-906, 1929

CHAPTER X

TUBERCULOSIS

The elementary facts concerning the tubercle bacillus and the general pathology of tuberculosis are so well known that it does not seem necessary to discuss them except for some phenomena which are of special importance in the pathogenesis of the cutaneous manifestations of internal tuberculosis

If the skin of a *normal*[709, 709-711] guinea pig is inoculated with tubercle bacilli the small wound heals primarily After a week an inflammatory reaction sets in A papule develops which during the third week forms an ulcer There is little tendency to heal and some ulceration or infiltration usually still exists when the animal dies of generalized tuberculosis. During the second week lymphangitis and lymphadenitis are marked The histological picture shows at first, an inflammatory reaction with many groups of tubercle bacilli During the third week tuberculoid structures start to form and the number of bacilli decreases so that only occasionally can single rods be found Tuberculin skin tests start to become positive about ten days after the infection Within four weeks the entire skin has become sensitized[710]

If the identical inoculation of tubercle bacilli is done in the skin of a guinea pig which at least four weeks *previously had been infected* with tuberculosis, an acute hemorrhagic edematous and sometimes necrotic reaction starts within twenty four hours reaches its height on the second day and then subsides rapidly After about ten days a necrotic hemorrhagic crust is thrown off After three to four weeks the lesion is usually healed There is no additional lymphadenitis and no further ulceration The histological examination reveals an acute inflammation The scab which contains the bulk of the bacilli comes off the underlying erosion heals and is soon covered with normal epidermis. Sometimes tuberculoid structures are formed earlier than in the primary inoculation It must be emphasized that this sequence of changes after primary and super infection known a *Koch s fundamental phenomenon* is subject to many variations and that great skill and experience are required to produce it in complete clarity This is particularly true[709] of the experimental hematogenous i.e. *intracardial* infection of the guinea pig

Two weeks after the intracardial injection of tubercle bacilli normal animals develop a papulo-squamous rash and die from generalized tuberculosis after four to five weeks. Tuberculous guinea pigs, however show during the second day a follicular rash which heals quickly after a latency of about two weeks

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[709] Lewandowsky, F Die Tuberkulose der Haut Berlin, 1916, Julius Springer

[710] Sulzberger M B and Wise F Tuberculin Newer Dermatological Considerations, Clin. North America 14 1934, 931

[711] Martenstein, H Neuere Ergebnisse auf dem Gebiet der Hauttuberkulose Die extrapulmonale Tuberkulose Vienna, 1933, Urban and Schwarzenberg

some papulocrustous lesions appear which heal spontaneously. The microscopic picture of the hematogenous lesion in the first infected animal is that of an inflammatory reaction of nonspecific character with abundant bacilli. The hematogenous lesions in superinfected animals are decidedly tubercular in structure, consisting of epithelioid and typical giant cells. There is periarterial necrosis but hardly any bacilli can be detected. The lesions are often found in the follicular plexus.[808] Similar tuberculoid lesions can be produced by the intracardial injection of killed tubercle bacilli.

The interpretation of these experiments and many variations has been formulated by J. Jadassohn[70] and his pupils, especially Lewandowsky, in a rule which has been amply confirmed not only in tuberculosis but also in many other infections. This so-called *law of J. Jadassohn and Lewandowsky* states that unchecked growth of microbes causes nonspecific inflammation. Where, however, microbes are locally and not too rapidly destroyed by the immunebiologic defensive reaction, tuberculoid structures develop. This law applies to the products of microorganisms.

Koch's fundamental phenomenon has been found valid in the human pathology. If the *skin of a person who has not had tuberculosis before is infected* with tubercle bacilli, a lesion characterized by rapid ulceration, lymphangitis and lymphadenitis and abscess formation develops in the course of one to two weeks.[713, 714] This syndrome, which is best known from the cases of circumcision tuberculosis[711, 715] but also from other traumatic infections,[71, 726] is called the primary complex of tuberculosis of the skin.

The number of bacilli in the ulcer is large so that they can be found in the direct smear. The tuberculin reaction is negative in the early stages but becomes positive three to eight weeks *after* the cutaneous infection (E. Löwenstein, after E. H. Urbach[721]). The tuberculous *primary complex* of the skin is much rarer than its pulmonary counterpart, the Ghon tubercle. Approximately one out of 750 cases of tuberculosis starts in the skin.[720, 722, 72]

Tubercle bacilli—for that matter also other *microbes—spread* very rapidly from a skin infection. Excision of a primary skin infection does not prevent

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For excellent pictures on experimental tuberculosis see Sulzberger, Dermatologic Allergy.[93] Pictures of moulages prepared under the direction of Drs. O. Mirecher and W. Jadassohn.)

[712] Palmstierna, K.: Post-traumatic Primary Tuberculous Infection of the Skin, Acta chir. Scandinav. 70: 249-259, 1932.

Brunsgaard, F.: So-Called Primary Complex of Tuberculosis of the Skin, Finska läk.-sällsk. Handl. 75: 5 2-537, 1933, Zbl. 44: 592.

[713] Kren, W.: Der tuberkulöse Primärkomplex der Haut, Zbl. 39: 1, 1932.

[714] Michelson, H. E.: Primary Complex of Tuberculosis of the Skin: Review of the Literature, Arch. Derm. & Syph. 32: 590-601, 1935.

[715] O'Leary, P. A., and Harrison, M. W.: Inoculation Tuberculosis, Arch. Dermat. & Syph. 44: 371-390, 1941.

[717] Wolff, E.: Über Vorhautlupus tuberkulose, Berl. klin. Wchnschr. 58: 1431, 1921.

[718] Finkelstein, L.: Ueber die Beschneidungstuberkulose, Kinderärztl. Prax. 3: 133-139, 1932.

[719] Fidler, H. K.: The Primary Cutaneous Tuberculosis Complex, J. A. M. A. 108: 2031-2034, 1937.

[720] Schuchardt, O.: Primary Tuberculosis of Skin in Children: Secondary Formation of Lupus, Arch. f. Kinderh. 116: 33-42, 1939.

[721] Michelson, H. E.: Allergy and Resistance in Tuberculosis, Journal-Lancet 62: 230-231, 1942.

[722] Rank, K. E.: Ausgewählte Schriften zur Tuberkulosepathologie, Berlin, 1928, Julius Springer.

[723] Ghon, A.: The Primary Complex of Human Tuberculosis, Am. Rev. Tuberc. 7: 314, 1923.

[724] Pollick, M. A.: Primary Cutaneous Complex: Inoculation Tuberculosis, J. Mt. Sinai Hosp. 6: 24-30, 1939.

systemic infection. Löwenstein was unable to prevent the generalization of a tuberculous infection from the hindleg of a guinea pig when he amputated the limb five minutes after the inoculation. A great number of similar observations have been made[illegible] showing that a truly local skin infection hardly exists. The primary tuberculous complex of the skin is of little practical, though of great theoretical importance. The majority of the tuberculous skin infections differ in two important points, from the primary complex. They occur in an already tuberculous and allergic organism and they are overwhelmingly autogenous and usually hematogenous These two facts help to explain many of the characteristics of the tuberculodermas

The *great variety* of clinical pictures of cutaneous tuberculosis is caused by the fact that neither the virulence of the tubercle bacilli nor the defense mechanisms of the human organism are powerful enough to bring about either a complete healing or a fatal course. The tuberculous infection can be compared to a war of position and attrition. J Jadassohn believed that superinfection is the most important factor in developing lupus from a tuberculous infection This has been widely accepted though some authors at least in some cases have placed more emphasis on the differences in the reactions of the infantile and adult human skins. Volk[illegible] sees an analogy in the difference of the primary tuberculous skin infection of the guinea pig which almost always develops an ulcerative and later generalized and fatal tuberculosis and the cutaneous infection of the rabbit in which the skin infection resembles lupus, remains localized and has a marked spontaneous healing tendency [illegible]

The *bovine* type of the tubercle bacillus causes about 13 per cent of all cases of skin tuberculosis[illegible] It has already been said that the *tuberculin skin test* becomes positive from three to eight weeks after the infection. The positive reaction is evidence of allergy against the tubercle bacillus and its products but it does not indicate immunity or resistance. The complete breakdown of the resistance as encountered in miliary tuberculosis and cachexia may be accompanied by a breakdown of other systemic functions e.g the ability to react with inflammation to the tubercle bacillus. In other words the tuberculin reaction may become negative This phenomenon is called *negative anergy* However measles influenza, and other infections, some forms of skin tuberculosis and especially the sarcoids[illegible] may prevent a positive reaction in an active

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*The term tuberculid has been avoided since it is confusing and unnecessary It can be considered accepted that all tuberculids are tuberculosis (Sulzberger and Goodman,[illegible]) and that microorganisms are demonstrable in practically all tuberculids (Wise and Sulzberger[illegible])

[illegible]Sulzberger M B., and Goodman J Tuberculodermas, M Clin North America 20 905-1007 1936.

[illegible]Wise F and Sulzberger M B Yearbook of Dermatology Chicago, 1935, The Yearbook Publishers, p 373

[illegible]Kallos, P and Kallos-Deffner L. L. Ueber Allergie- und Immunitätsverhältnisse bei Hauttuberkulose Zbl 49: 273-298, 1933.

[illegible]Dietz, J Ueber die Typen der Tuberkelbacillen (TB) bei Hauttuberkulosen, Arch f Dermat Syph 179: 380-398, 1939

[illegible]Zieler and Hämel Hauttuberkulose in ihren Beziehungen zur Tuberkulose innerer Organe, Ergebn d ges Tuberk Forsch 6 438, 1934

[illegible]Pinner M Non-Caseating Tuberculosis, Am Rev Tuberc. 37 690, 1938

way by production of inhibiting substances which are called anticutins.[731, 732] This is called *positive anergy* In such cases the resistance to infection e.g with the bacillus Calmette-Guérin may be very high [732] The conception of positive anergy is based on the noncachectic cases with positive tuberculosis and one of the mentioned conditions especially the sarcoids, in which the tuberculin reaction is negative [733, 734]

The methods of skin testing for tuberculin allergy are the same as those used in testing other kinds of allergic conditions

1 The intracutaneous injection [735, 736] This test is very accurate in J Jadassohn s graded quantitative method which consists of the simultaneous intradermal injections of 0 1 c.c. of dilutions of old tuberculin—Koch (OTK) in concentrations of 1 1 000 000 1 100 000 1 10 000 and in some cases 1 100 and 1 10 and control saline wheals.[733] More often purified protein derivative (PPD) is used This is available in convenient tablets of two strengths which have to be dissolved in 1 c.c. of diluent. One-tenth cubic centimeter of fresh first strength solution (0 000 or mg) is injected first. If no reaction within 48 hours occurs 0 1 c.c. of fresh second strength solution (0 005 mg) is injected into the other arm

2 The scratch or abrasion test (von Pirquet)[737] with OTK.

3 The inunction of a 50 per cent tuberculin lanolin salve [738]

4. The patch test [739, 740]

> For the technique of these tests, the reader is referred to textbooks of allergy and tuberculosis for comparative evaluation to E. Friedman, M H Black and A. L. Esserman, M. Sulzberger and F Wise. [89]

The patch test is a convenient and sufficiently reliable method for preliminary information Urbach[148] advises following up a patch test which is negative after one week with the more sensitive Mendel-Mantoux test. In all tests the reaction can be considered positive if an inflammatory papule of at least 5 mm in diameter develops. The papule reaches its height in forty eight to seventy two hours and then slowly fades *Immediate reactions are not specific*

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[731] Kemal, F Hauttuberkulose Ter Zpravy 6 137 1[illegible] franz Zusammenfassung 190 107 1934 Zbl 89 [illegible]

[732] Pinner M Weiss, M and Cohen A. C Procutins and Anticutins, Yale J Biol & Med. 15 459-462, 1943

[733] Martenstein, H and Noll R Statistische U ntersuchungen über die Tuberculin Reaction, Arch. f Derma Syph 1[illegible] 409 1929

[734] Loewy H Boeck Sarcoid and Lupus Pernio Dissertation, Breslau 1931

[735] Mendel F Die Pirquet sche Hautreaktion und die intra enöse Tuberkulinbehandlung, Med Klin 4 402-404 1908

Mantoux C I tradermo-Tuberkulin Reaction, München med Wchnschr 55 2117 1908

[737] Von Pirquet C Tuberkulindiagnose durch cutane Impfung, Berl klin. Wchnschr 44 644 1907

[738] Moro E Ueber eine diagnostisch verwertbare Reaction der Haut auf Einreibung mit Tuberculinsalbe München med Wchnschr 55 216 1908.

[739] Nathan E and Kallos, F Ueber eine epicutane Tuberkulinreaktion bei Hauttuberkulose, Klin Wchnschr 1931 II 2392 2393

[740] Vollmer H and Goldberger E W A New Tuberculin Patch Test Am. J Dis. Child. 54 1019 1937

[741] Friedman, E Black, M H., and Esserman, A L. Tuberculin Tests, Am. J Dis. Child. 46 59-65, 1933.

A *positive reaction* in children under seven years is generally a sign of active tuberculosis. Beyond seven years the positive test must be correlated with the clinical picture In adults a positive test does not prove more than the well known fact that almost everybody once in his life becomes infected with tuberculosis. In the vast majority of the cases the disease becomes arrested after the primary stage leaving behind an allergy to tuberculin.

A *negative tuberculin test* especially the Mendel Mantoux test must with the mentioned exceptions, be interpreted as indicative of the absence of a tuberculous infection of more than 8 weeks.

Hematogenous Skin Tuberculosis

Skin tuberculosis may develop by ectogenous inoculation into the skin and by endogenous infection The tuberculosis verrucosa cutis of the hands in slaughterhouse workers the postmortem wart and the lupus of the buttocks in small children who sit on the floor of a tubercle bacilli-infected room are examples of ectogenous tuberculous skin infection The endogenous infection of the skin plays a more important part. Endogenous lupus by contiguity from underlying tuberculous lymph nodes especially of the neck is a common occurrence in countries where skin tuberculosis is more frequent than in America. The lymphogenous spread of lupus is known However compared with these ways of infection the hematogenous tuberculous infection of the skin is far more important. Foci of tuberculous infection which are capable of releasing tubercle bacilli into the bloodstream are very common Even old calcified lymph nodes may still contain virulent tubercle bacilli as has been shown in autopsies of patients who for many years suffered from hematogenous crops of lupus. It is more difficult to explain why there is so little hematogenous skin tuberculosis in view of the frequency of the foci and of the bacilli in the blood than it is to give reasons for the hematogenous nature of many cases of cutaneous tuberculosis. It can be considered a fact that more than 50 per cent of the lupus cases are caused by hematogenous infection [741] mostly from pulmonary or lymphatic foci.[742]

The *relationship of pulmonary tuberculosis* to *cutaneous tuberculosis* has been the subject of many investigations. Pulmonary tuberculosis has been found existing simultaneously with skin tuberculosis, especially lupus vulgaris in percentages differing as widely as 8 and 90 per cent. An analysis of 300 lupus cases in Münster Germany [743] showed 12 per cent more or less active and 60 per cent inactive pulmonary tuberculosis while in a control group of about 5000 German university students only 1 per cent active and 18 per cent inactive lung cases could be found. St. Epstein[744] determined 16 per cent as the incidence of active pulmonary tuberculosis in 200 lupus patients In 429 fatal lupus cases visceral usually pulmonary tuberculosis was the cause of death in

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[741] Kremer E. Untersuchungen über Hauttuberkulose Würzburg Abh Bd 27 H 3, 1931
[742] Rauschkolb J E Tuberculosis of the Skin, Arch Dermat. & Syph 29 399-406 1934.
[743] [illegible], W Lungenbefund bei 300 Lupuskranken, Ztschr f. Tuberk 70 54-60, 1934.
[744] Epstein, St Tuberculosis of Lungs in Patients With Sarcoidosis, Granuloma Annulare and Lupus Erythematosus, Arch Dermat & Syph 42: 1 10, 1940

48 per cent.[744] From these and many other statistics it can be concluded that the incidence of lung tuberculosis in lupus is a high one. On the other hand the percentages of skin tuberculosis in very large groups of tuberculous patients has always been found low: 0.2 per cent,[747] 1 per cent in 27,540 cases,[74] less than 2 per cent in 18,000 cases.[749] This compares well with many older statistics[386] and seems to bear out the old rule that lupus patients often become consumptive *but that consumptives rarely develop lupus.* While the figures seem to be very low, the incidence of skin tuberculosis is still about 2 to 3 times higher in patients with pulmonary tuberculosis than in a comparable normal group. Similar tendencies as in the relationship of lupus and pulmonary disease prevail in its relation to surgical tuberculosis. Among 275 lupus cases were 16 per cent with bone or joint tuberculosis while among 371 cases with tuberculosis of the bones and joints only 5 per cent had lupus.[750] The isolation of tubercle bacilli from the *blood* either by animal inoculation or by culture with the Löwenstein method has recently been more often successful than was held possible before. It is true that many observers could not obtain the same results as Löwenstein.[759] The positive findings however carry more weight than the negative ones. Kren[386] could show that if blood culture of patients with lupus vulgaris, erythema induratum and lupus erythematosus was done more than seven times, positive cultures could be found in all cases. The frequently negative blood cultures are most likely due to technical difficulties, to unfavorable time of testing and to the too small numbers of the investigations. In Kren's[386] series the blood specimens, up to nineteen different ones from one patient, were sent to Löwenstein without diagnosis. It is believed that the irregularity of the showers of bacilli appearing in the blood is responsible for the inconstant findings. However with or without confirmation[752] of all of Löwenstein's findings the frequent occurrence of tubercle bacilli in the blood of patients with skin tuberculosis is a fact.[353 416 753-759]

[746] Stoempke, G. Skin Tuberculosis, Causes of Death. Arch. f. Dermat. & Syph. 183: 216-222, 1942.

[747] Griesbach, R. Hautkrankheiten bei der Lungentuberkulose mit besonderer Berücksichtigung der Akne, Ztschr. f. Tuberk. 57: 406-416, 1930.

[748] Baán, S. J. Skin Disease in Pulmonary Tuberculosis, Dermatologica 86: 17-48, 1943.

[749] Gáll, O. Clinical Types of Pulmonary Tuberculosis Associated With Skin Tuberculosis, Tuberkulózis 1: 253-259, 272-279 (Hungarian with German summary). Zbl. 47: 242.

[750] Meyer, J. Tuberkulose als Organsystemerkrankung, Acta tuberc. Scandinav. 9: 67-288, 1935. Zbl. 65: 500.

[751] Kolle, W. and Küster, E. Tuberkelbacillen im strömenden Blute, Deutsche med. Wchnschr. 1934 I: 309-313.

[752] Rubin, E. H. Haematogenous Tuberculosis in Adult. Generalized Hematogenous Tuberculosis, Am. Rev. Tuberc. 39: 557-586, 1939.

[753] Wilson, G. S. Tuberculous Bacillaemia, Medical Research Council, Special Report Series, N. 182, London, 1933.

[754] Mathieson, A. F. Resultat mit der Loewensteinschen Blutkulturmethode bei verschiedenen Formen der Hauttuberkulose, Wien. klin. Wchnschr. 45: 719-720, 1932.

[755] Ilbuchi, T. Züchtung von Tuberkelbacillen aus strömendem Blut, Schweiz. med. Wchnschr. 1933 I: 307-310.

[756] Popper, H., Bodart, F. and Schindler, W. Tuberkelbacillenzüchtung aus dem Blut. II. Virchows Arch. f. path. Anat. 290: 616-637, 1933.

[757] Cournant, P., Gaté, J. and Michel, P. J. Bacillémie tuberculeuse et tuberculose cutanée, Presse méd. 42: 497-499, 1934.

[758] Ora, A. Sul valore del metodo Löwenstein per lo studio della bacillemia, nelle tubercolosi cutanee nelle tubercolidi, Arch. ital. di dermat. 13: 3-18, 1937.

[759] Löwenstein, E. Tuberculous Bacillemia and Its Significance in Medicine, Quart. Bull. Health Organ. League of Nations 4: 619-633, 1935.

The start of cutaneous tuberculosis in the intima of veins was demonstrated a long time ago[11] The distribution of the lesions in the cases of post-exanthematic lupus[100] hardly allows any other explanation than general spread by the circulation with selective take in some sites and failure to take in others (see chapter on hematogenous skin infection)

Blood borne infection may lead to all of the well-known pictures of skin tuberculosis. While hematogenous infection is the cause of the papulonecrotic and indurative types of tuberculosis and of the majority of the lupus vulgaris cases, it is much less common in scrofuloderma and only few instances have become known in tuberculosis verrucosa cutis.

Cutaneous Tuberculosis

The primary lesion of *lupus vulgaris* regardless whether of endogenous or ectogenous origin is the *lupus nodule* as it is called though it is usually only a *macule* In its early and uncomplicated stage this is a pinhead to lentil-sized red or copper-colored smooth spot. Under glass pressure the spot does not fade and the blanching of the surrounding skin makes it stand out more clearly in a red brownish or dark yellow color In suitable light it is strikingly trans-



Fig 93 — Lupus vulgaris (nodules) Courtesy Dr M Jessner)

parent which is responsible for the often used comparison with apple butter If one gently tries to penetrate the surface with a fine bulbous probe one is surprised how easily the instrument sinks into the soft tissue at a degree of pressure which would not be sufficient to pierce normal skin Such early lupus nodules are most commonly seen on the face particularly on and around the nose The great variety of pictures which may be encountered during the course of lupus vulgaris can be explained by a number of factors the dominant role of any one being able to create a clinical variety Increase in number and coalescence of the spots may lead to extremely chronic patches of flat lupus which may be as small as pea or cover entire regions. Such large *flat lesions*

[100] Artom, M Tubercolosi cutanee post-morbillose Arch. ital. di dermat 8 [illegible] 1933

48 per cent.[746] From these and many other statistics it can be concluded that the incidence of lung tuberculosis in lupus is a high one On the other hand the percentages of skin tuberculosis in very large groups of tuberculous patients has always been found low 0.2 per cent [747] 1 per cent in 27,540 cases [748] less than 2 per cent in 18 000 cases.[749] This compares well with many older statistics[300] and seems to bear out the old rule that lupus patients often become consumptive but that consumptives rarely develop lupus. While the figures seem to be very low the incidence of skin tuberculosis is still about 2 to 3 times higher in patients with pulmonary tuberculosis than in a comparable normal group *Similar tendencies as in the relationship of lupus and pulmonary disease* prevail in its relation to surgical tuberculosis Among 275 lupus cases were 16 per cent with bone or joint tuberculosis, while among 371 cases with tuberculosis of the bones and joints only 5 per cent had lupus.[750] The isolation of tubercle bacilli from the *blood* either by animal inoculation or by culture with the Löwenstein method has recently been more often successful than was held possible before It is true that many observers could not obtain the same results as Löwenstein [751] The positive findings however carry more weight than the negative ones. Kren[55] could show that if blood culture of patients with lupus vulgaris erythema induratum and lupus erythematosus was done more than seven times positive cultures could be found in all cases. The frequently negative blood cultures are most likely due to technical difficulties to unfavorable time of testing and to the too small numbers of the investigations. In Kren's[55] series the blood specimens, up to nineteen different ones from one patient were sent to Löwenstein without diagnosis. It is believed that the irregularity of the showers of bacilli appearing in the blood is responsible for the inconstant findings. However with or without confirmation[752] of all of Löwenstein's findings, the frequent occurrence of tubercle bacilli in the blood of patients with skin tuberculosis is a fact.[55-56-416 753-759]

[745] Scheurapke, G Skin Tuberculosis, Causes of Death. Arch f. Dermat & Syph. 183 216-222 1942.

Griesbach, R Hautkrankheiten bei der Lungentuberkulose mit besonderer Berücksichtigung der Akne, Ztschr f Tuberk. 57 406-416 1930

[748] Szántó J Skin Disease in Pulmonary Tuberculosis, Dermatologica 88 17-42, 1943

[749] Gáll, G Clinical Types of Pulmonary Tuberculosis Associated With Skin Tuberculosis, Tuberkulózis 1 252-259 272-279 [Hungarian with German summary] Zbl 47 283.

[750] Meyer J Tuberkulose als Organsystemerkrankung. Acta tuberc. Scandinav 9 67 288, 1935; Zbl. 85 809

[55] Kolle W and Küster E Tuberkelbacillen im strömenden Blute, Deutsche med Wchnschr 1934 I 309-313

[752] R bin, E H Haematogenous Tuberculosis in Adult Generalized Hematogenous Tuberculosis, Ala Rev Tuberc 30 557-586 930

[753] Wilson, G S Tuberculous Bacillemia, Medical Research Council, Special Report Series, No. 182, London, 1933

[754] Mi klosen, A F *Resultat mit der Loewensteinschen Blutkulturmethode bei verschiedenen* Formen der Hauttuberkulose, Wien. klin W hnschr 45 719-720 1932

[755] Ilbach, T Züchtung von Tuberkelbacillen im strömenden Blut, Schweiz. med Wchnschr 1933 I 307-310.

[756] Popper H Bedart, F and Schindler W Tuberkelbacillenzüchtung aus dem Blute II Virchows Arch f path Anat. 290 616-637 1933

[757] Courmont, P Gaté J and Michel, P J Bacillémie tuberculeuse et tuberculose cutanée, Presse méd 42 497-499, 1934

[758] Oro, A *Sul valore del metodo Löwenstein per lo studio della bacillemia, nella tubercolosi cutanea nelle tubercolidi, Arch ital. di dermat 13 3-18, 1937*

[759] Löwenstein, E Tuberculous Bacillemia and Its Significance in Medicine, Quart. Bull. Health Organ., League of Nations 4 619-632, 1935

Fig. 97

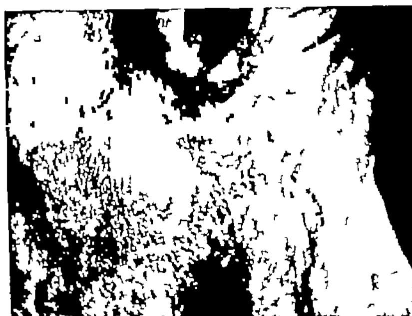




Fig. 98

Fig. 97.—Lupus vulgaris surrounding the ear lobe. Exceedingly chronic course; note worn off ear lobe.

Fig. 98.—Lupus vulgaris. A flat small lesion had been excised and the defect covered by full-thickness transplantation. Recurrent lupus lesions did not invade the transplant. Yellowish lesions

are often scaly so that they may resemble psoriasis this is still more likely if the outlines are circinate The tuberculous tissue may grow above the skin level and form elevated hypertrophic and even fungating or tumorlike granulations *Lupus hypertrophicus* lupus tumidus and other terms describe this variety which usually involves the nose the lips and the lobe of the ear



Fig [illegible] —Lupus vulgaris (Courtesy Dr M Jessner)

Ulceration and crust formation are more often a feature of the hypertrophic than of the flat forms. In the latter the ulceration is usually shallow and more marked along the edges. The healing tendency and scar formation vary though healing is rarely complete The lupus may spread with an active *serpiginous* edge over large areas leaving in its wake a scar which usually contains some lupus nodules. Such annular or gyrate lesions may resemble syphilis or ringworm The face may gradually become scarred shrunken and immovable and the conjunctiva and finally the eye itself may be destroyed The mouth may be reduced to a small rigid hole Such terminal stages may equal leprosy in dreadfulness. Cancer is not an uncommon complication The suffering of such patients is beyond description Such cases are fortunately rare especially in America but they can be seen in numbers in all the European *lupus hospital This tragic outcome however is an exception In the vast* majority of the cases the lesions are stationary or slowly progressive and often

amenable to treatment. Recurrences are very common Spontaneous regression occurs but is rarely complete.

The *histology* of the lupus nodule shows a conglomeration of typical tubercles with epithelioid cells giant cells lymphocytes and central necrosis, the latter often not particularly marked The same factors which by their dominance decide the clinical picture also produce a great histological variety



Fig. 100 Lupus vulgaris (Courtesy Dr Garrett Cooper)

It is now almost generally accepted that *lupus is the expression of a cutaneous tuberculous superinfection* with own or other tubercle bacilli. Existing tuberculosis shapes a tuberculous infection of the skin into lupus thus making it a *manifestation of an internal disease* Lupus vulgaris starts in 55 per cent of the cases during the first two decades of life[illegible] a fact which is not easy to explain Scrofuloderma and children s diseases l ke measles *may play* a part though convincing cases are not very common the postexanthematic lupus is a good example of hematogenous lupus[illegible] It is not too rarely seen to start shortly after or even during the measles and also after other acute exanthems. The postexanthematic lupus is often disseminated and appears simultaneously in several or many spots Artom[illegible] suggests that the anergy during measles favors the development of postexanthematic lupus. The prognosis is relatively good since the seeded lesions usually remain inacti e[illegible]

[illegible] Zieler K Primary Appearance of Chronic Skin Disease at Various Ages, With Special Reference to Lupoid Tuberculosis Arch f Dermat Syph 183 297-303, 1942

[illegible] Leiner C and Spieler F Ueber disseminiert Hauttuberkulose im Kindesalter Ergebn d inn Med 7: 1911

Lupus miliaris disseminatus (Lupus follicularis Tilbury Fox 1878) is a follicular form of lupus which almost always affects the face only It has a great similarity to acne and rosacea. In fact most cases go under these diagnoses for a long time After an initial stage of erythema has passed follicular papules develop often with scales a yellow center erythema and subcutaneous nodules. The lesions are distributed over the nose the cheeks the chin and though less pronounced the forehead and other parts of the body On close *diascopic inspection* the apparently pustular efflorescences show typical lupus tissue The lesions appear in crops do not coalesce do not contain pus and have a marked healing tendency The histological picture is that of typical tuberculosis. The distribution in the perifollicular vascular plexus and other histological findings prove the hematogenous character Tubercle bacilli have rarely been found in the lesions Pulmonary and other visceral tuberculosis has been found in a considerable number of the cases but the tuberculin reaction is often weak. The prognosis of the condition itself[193] is favorable and it responds well to peeling with strong ultraviolet light



Fig 101 Tuberculosis verrucosa cutis Courtesy the late Dr W A Pusey from Sutton and Sutton Diseases of the Skin The C V Mosby Company)

Tuberculosis verrucosa cutis starts as a firm prominant nodule differing from lupus by the lack of transparency and the great resistance to the piercing probe The papules increase peripherally coalesce but little become hyperkeratotic and later verrucous Follicular abscesses are common especially in lesions which have reached more than coin size and greater thickness. The patches may reach great size They are frequently seen over the bony prominences of the hands and feet The right hand is most often affected[194] The knuckles and the ankle areas are affected only occasionally The lesion are mostly single or few in number but hematogenous dissemination with many

[193] Peck S M Lupus Miliaris disseminatus faciei, Arch f Dermat u Syph 160 845-855 1930

[194] Ledermann, K O Statistische Untersuchungen über Tuberculosis verrucosa cutis, Arch f Dermat Syph 167: 103-105, 1932.

lesions has been seen There is a decided preponderance of the male sex because the disease is often an occupational infection of slaughterhouse workers who are usually males but occasionally the disease also occurs in other persons who have contact with tuberculous material The occupational character accounts for the common distribution on the hands and feet. It also occurs as an autogenous



Fig 102.—Scrophuloderma (Courtesy Division of Dermatology Department of Medicine University of Chicago)

superinfection with the sputum of patients with pulmonary tuberculosis The bovine type of the tubercle bacillus has been found in 50 per cent or more of the cases, and bovine infection is probably responsible in all slaughterhouse cases.

Volk states that no explanation could be given why in one case tuberculosis verrucosa and in other cases lupus results from superinfection Probably in spite of exceptions, the terrain of the hands and feet which has a greater keratotic tendency than other parts is one of the influencing factors This is illustrated

by cases of hematogenously disseminated skin tuberculosis with tuberculosis cutis verrucosa on the acra and lupus on the face.[300, 721]

The close similarity of tuberculosis verrucosa cutis and some phases of blastomycosis must be emphasized. Verrucous tuberculosis has a greater tendency to heal than lupus vulgaris and the response to treatment is more complete. The microscopic picture is that of tuberculosis but combined with parakeratosis and hyperkeratosis. Lymphangitis is a frequent complication.



Fig. 103. Tuberculosis cutis colliquativa (scrophuloderma). (Courtesy Dr. M. Jessner.)

Tuberculosis colliquativa (*scrofuloderma*) is a cold abscess of the skin, most frequently originating in a subcutaneous tuberculous focus, usually a lymph node or bone. It starts as a subcutaneous nodule which becomes adherent to the skin and forms an abscess or sinus without acute symptoms. Several such lesions may coalesce into a network of sinus abscesses, scars and ulcers, not infrequently surrounded by lupus. The most common site of scrofuloderma is the neck with its great number of easily infected lymphatic nodes. Tuberculosis of the sternum and of the ribs are other starting points for colliquative tuberculosis of the skin. Children and young adults are most often affected. Scrofuloderma occurs occasionally, mostly in young children, in a hematogenous

distribution without connection with underlying structures These cases closely resemble the corresponding phases of sporotrichosis blastomycosis and coccidioidomycosis. The prognosis of scrofuloderma and the therapeutic response is usually good though the process may last several years

Ulcerative tuberculosis of the orifices in pulmonary or genitourinary tuberculosis produces characteristic lesions most often found on the tongue and around the anus but also on the lips the ears and the glans penis. On the tongue the lesions may appear as shallow jagged oblong round or rhagadiform ulcers the papular primary stage of which is seldom seen The floor of the ulcer is granulated and yellowish the edge slightly undermined The lesion progresses by a coalescence with minute pustular lesions in the surroundings. There is little induration and sometimes surprisingly little sometimes surprisingly severe pain. Perianal ulcerative tuberculosis occurs in 5 to 10 per cent of patients with pulmonary tuberculosis. All abscesses and fistulae in such patients must be considered suspects.[785, 786]



Fig 101 — Tuberculous ulcer of the tongue in pulmonary tuberculosis

This ulcerative type of lesion contains more tubercle bacilli than the other forms *In line with this fact is the frequent absence of typical tubercular structures* and the dominance of nonspecific inflammation Ulcerative tuberculosis of the tongue is more frequently seen in men than in women

Tuberculous ulcers of the orifices are important indicators of visceral especially pulmonary tuberculosis [787–789]

[785] Garnes, E [illegible] Perianal Tuberculosis Quart Bull [illegible] 4 448–452, 1930

[786] [illegible] R M [illegible] Fistula Clin North America 17 [illegible], 1937

[787] [illegible] R and Miller J W Tuberculosis of the Tongue Report of Three Cases J A M A 96 97 100 1930

[788] Nicolas J and [illegible] P [illegible] de la langue Bull Soc franç de dermat et syph 37 [illegible] 1930

[789] [illegible] P [illegible] Dermosifilografo 7 [illegible] 1932

While the forms of cutaneous tuberculosis so far mentioned start predominantly from single lesions the following varieties have in common an

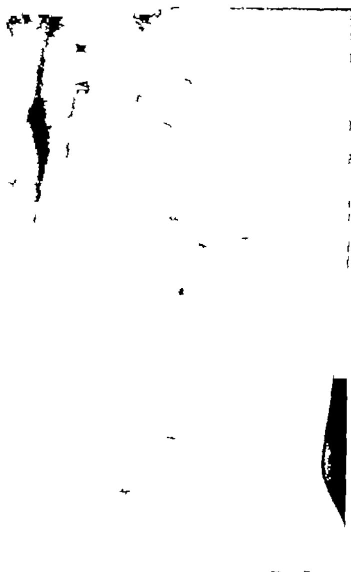


Fig 103 Lichen scrofulosorum (tuberculosis lichenoides) in [illegible] patient (Courtesy D M Jessner)

exanthematic though not always copious distribution Number and distribution have more importance than the features of the individual lesions which are usually small and not destructive

Miliary tuberculosis of the skin is almost exclusively seen in infants and young children [770, 771] In adults the miliary foci are numerous in the subcutis but do not reach the skin The rash consists of pinhead sized hardly prominent, often hemorrhagic and slightly umbilicated papules. These lesions are quite dense in some areas. They may heal spontaneously leaving a slightly depressed pigmented spot. The exanthem is inconspicuous and may easily be overlooked [772] The diagnosis is rarely made without biopsy The histologic structure is not so much tuberculoid as inflammatory in character There are tremendous numbers of bacilli Small vessels are sometimes solidly packed with bacillary emboli[772] and surrounded by necrosis, but there is a vast misproportion between the number of bacilli and tissue defense [772] The tuberculin reaction is sometimes negative [773] Hoyle and Vaizey[774] list about 16 per cent tuberculous skin manifestations in their series of 120 cases of miliary tuberculosis. The prognosis is hopeless.

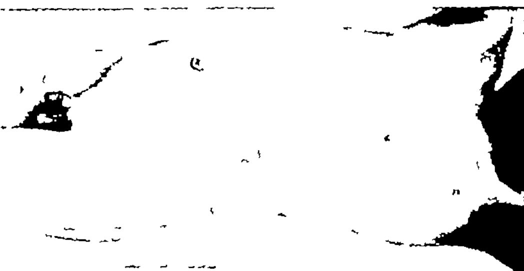


Fig 66 —Lichen scrofulosorum (Courtesy Dr Erich Urbach)

In *tuberculosis lichenoides* or lichen scrofulosorum large numbers of micropapular mostly follicular often conical and keratotic skin colored or pink to yellowish brown lesions are grouped in round oblong or irregular patches They are mostly found on the back, particularly in the lumbosacral region and on the abdomen The lesions develop slowly and patches may persist for years Older lesions often have a scale and if they are packed very closely together in old plaques, a large desquamating surface may give a

[770] Gerlach F Die Beteiligung der Haut bei Miliartuberkulose Virchows Arch. f path. Anat. [illegible] 601-609 1932
[771] Koch H Die Tuberkulose des Säuglingsalters, Ergebn d inn Med. u Kinderh [illegible] 1913
[772] [illegible] R [illegible] tuberkulose [illegible] 41 [illegible]
[773] [illegible] E Tuberculosis cutis miliaris acuta generalisata im Kindesalter Jahrb f Kinderh [illegible] 24-25 1931
[774] Hoyle and Vaizey Chronic Miliary Tuberculosis London, 1937 Oxford University Press

psoriasiform appearance Usually the center of such plaques is less scaly than the edges but more grater or chagreen leather like In some cases some or all of the papules bear a hard sharp horny little spine The microscopic picture shows almost invariably tuberculoid structures without or with very few bacilli

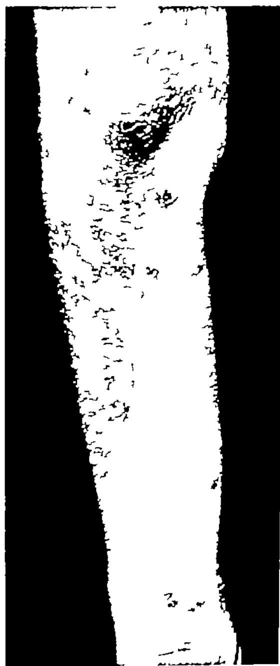


Fig 107 Papulonecrotic tuberculosis (Courtesy Division of Dermatology Department of Medicine University of Chicago)

Phlyctenular conjunctivitis is a frequent accompaniment. The dermatosis is of great [illegible] symptomatic significance. It indicates, almost always the existence of internal tuberculosis, usually of a more benign type. The dermadrome is rare in adults more common in children It frequently makes its appearance after measles and other acute infections. However there are great geographic differences. Tuberculosis cutis lichenoides is a common sight in the European skin clinics while in North America and particularly in the tropics and subtropics it is like all types of skin tuberculosis either rare or nonexistent[illegible] (Pusey after Volk[illegible])

Tuberculosis papulonecrotica This variety of cutaneous hematogenous tuberculosis has been described under a score of names[illegible] among which the odd terms folliclis and acnitis are still being used because they were given by the first describer T Barthélemy The term tuberculid is also often applied

The evolution of the lesion is simple and characteristic. A cutaneous nodule of linseed size grows within about four weeks to its maximal size which does not exceed that of a cherry stone and becomes a movable firm well defined slightly raised dusky bluish red or brown papule. The center of the fully developed papule shows a yellow head which however does not contain pus as one might expect, but a rather tough necrotic core which may come out by itself leaving a small punched-out ulcer More often a deep necrotic scab is formed which comes off after two to four weeks, producing a small crater shaped scar with sharp steep pigmented edges The scars are often more characteristic than the active lesions. Papulonecrotic tuberculosis is usually fairly evenly disseminated over the arms hands, and legs, and occasionally the trunk. The extensor surfaces the skin about the joints and the buttocks are more often affected but no area is immune.

Genital lesions may suggest secondary syphilis.[illegible] Barthélemy called acnitis a deeper situated acneiform papulonecrotic tuberculosis of the face. This condition is closely related to lupus miliaris faciei. The lesions of papulonecrotic tuberculosis appear in crops and have a much more marked spontaneous healing tendency than other forms of skin tuberculosis. This type of skin tuberculosis is less responsive to tuberculin than is lupus.[illegible] The microscopic structure is tuberculoid Tubercle bacilli are scarce but have quite often been found particularly in children [illegible]

Combination with pulmonary and other forms of tuberculosis including skin tuberculosis is the rule

Tuberculosis indurativa (Erythema induratum Bazin's disease) is a rather rare dermatosis characterized by cutaneous or subcutaneous nodules or plaques of much larger size than in the papulonecrotic lesions. There are usually only a few lesions scattered over both legs especially the calves and rarely also over the posterior aspects of the thighs the buttocks, the forearms or the face They start as indolent nodules, which grow within several weeks, to almond or even

[illegible] Incidence of Tuberculosis of the Skin, Arch Dermat & Syph [illegible] 130-134, 1942
[illegible] Barthélemy [illegible] L Arch de T Barthélemy Arch dermat-syph Hôp St. Louis [illegible] 1937
[illegible] Superficial Papulonecrotic Tuberculid [illegible] Negro, Arch Dermat & Syph 47 [illegible] 1943

palm size Such fully developed lesions are visible as a pink or lavender smooth erythema resembling the lilac ring of scleroderma Palpation reveals an indurated plaque of varying depth which is sometimes connected with cordlike phlebitic changes. The infiltrate is movable with the skin and usually is not tender In larger lesions the center is depressed or it may though rarely become ulcerated and then resemble a syphilitic gumma The plaques heal spon



Fig 108



Fig. 109

Fig 108 Tuberculosis indurati (erythema induratum) (Courtesy Dr M Jessner)
Fig 109 Tuberculosis ind rati (erythema induratum (Courtesy D M Jessner)

taneously but the course may take many weeks months or even years if ulceration occurs The oral mucosa is occasionally involved [771, 77] The dermadrome is many times more common n the female than in the male sex New crops are usually observed *during the winter nd pring* [772] The tuberculin reaction is strongly positive *Tubercle bacilli are rarely found in the lesions* The struc

[771] Schidlachl, J Erythema indura m, Arch f Derm & Syph 90 371 1908
[772] Forster A Erythema induratum, Arch f Dermat Syph 103 90 1927

ture is decidedly tuberculoid Combination with visceral tuberculosis and with other forms of cutaneous tuberculosis is not rare.[illegible]

Rosacea-like Tuberculosis Lewandowsky[illegible] described this form of skin tuberculosis which in the majority of cases is seen in women[illegible] of 30 to 60 years of age. The disorder develops gradually The typical case shows a great number of papules, mostly follicular scattered symmetrically over the cheeks and forehead often leaving the nose and chin free. The papules are small to medium sized with a decided yellowish brown tinge and do not completely



Fig. 110 — Rosacea-like tuberculosis (Lewandowski) Note spots which become more distinct under glass pressure. (Courtesy Division of Dermatology Department of Medicine, University of Chicago.)

fade under the pressure of glass. The diascope does not however show the transparent apple jelly colored lupus nodule as in lupus miliaris which it resembles. There may be some pustulation cyanotic erythema and a certain amount of telangiectasis but not as marked as in rosacea Scaling is sometimes present [illegible]

[illegible] Lewandowsky F Rosacea-ähnliche Tuberculide des Gesichts, Cor.-Bl f schweiz Aerzte 47 1280, 1917

[illegible] Wile U J and Graner F H Rosacea-like Tuberculosis (5 Cases) Arch Dermat & Syph. 31 174-180 1935

[illegible] Michelson H E and Wiser L H Tuberculodermas of the Face Arch Dermat & Syph 29 280-290, 1934

[illegible] MacKee G M and Sulzberger M B Rosacea-like Tuberculid of Lewandowsky Arch. Dermat & Syph 31 160-178, 1935

The microscopic structure is tuberculoid. No bacilli seem to have been found in the lesions so far The patients are usually though not always [781] highly sensitive to tuberculin which is in contrast to the reaction in lupus miliaris. Visceral or other cutaneous tuberculosis, mostly of benign character was found in a fraction of the cases Though still rare rosacea like tuberculosis is a relatively frequent form in America [778]

CHAPTER XI

DERMATOSES WITH CLAIMED BUT STILL CONTROVERSIAL TUBERCULOUS ETIOLOGY

Erythema Nodosum

Erythema nodosum is a uniform syndrome characterized by an acute eruption of cutaneous and subcutaneous nodules together with systemic symptoms, especially fever The nodules are mostly found in the tibial areas, less often on the extensor surfaces of the forearms and rarely on the face [733] They are not very numerous from a few to about thirty varying from pea to walnut size sometimes moderately raised above the skin level They are quite painful to the touch The more superficial lesions are pink to red and undergo a change of colors which resembles bruises (erythema contusiforme) There is little tendency to coalesce The nodules appear in several crops each of which takes about 1½ to 2 weeks to heal The entire attack may last from three to six weeks or longer Recurrences occur frequently

The outbreak is often preceded and accompanied by fever respiratory and gastrointestinal symptoms and pains in the muscles and joints which are sometimes swollen The prognosis of the dermatosis, as such is favorable

The incidence shows a marked preponderance of *children* and adolescents over the adult and of the adult *female over the male.*[732] Erythema nodosum is seen more frequently in the *cold season.* There seems to be a high susceptibility of the nordic races.

There are many reasons to relate erythema nodosum with a tuberculous infection.

Tubercle bacilli have lately been detected more frequently in the lesions rarely and not[734, 737, 48] undisputedly in microscopic sections but more often by successful inoculation into the guinea pig [87, 738, 736] Debré Mignon Mallet[739]

Literature up to 1929, see P Tachau [732]

[732] Tachau, P Erythema exsudativum multiforme und Nodosum, Handb d H Gk, 6, 2 584-654 1928.

[733] Bierfarb, S M and Morris G E Erythema Nodosum of Face Arch Dermat. & Syph. 43 803-804, 1941

[734] Millman G and Bredler L Skin Tuberculosis, Review of Recent Literature Paris méd 1 9-87 1930

[735] Cibils A B Tuberculous Primary Infection of the Skin and Secondary Erythema Nodosum. Arch argent de pedia 7 00-48, 101 70 1936 Zbl 54 643

[736] Saenz A Chevallier P Lévy Bruhl, M and Coutl, L. Sur la présence du bacille de Koch virulent dans les lésions cutanées et dans le sang d une malade en pleine accès d érythème noueux Compt rend Soc de biol 112: 941-943 1933

[737] Arena, A A Existence d Mycobacterium tuberculosis dans les nodules de l érythème noueux Compt rend. Soc de biol 115 340-342, 1934

[738] Saenz, A and Broca R Récherches bactériologiques sur l érythème noueux Bull Soc franç. de dermat et syph 43 11 1100-11 1 1935

[739] Debré R Mignon, M and Mallet R L examen radiologique du thorax au cours de l érythème noueux Bull Soc franç de dermat et syph 43 11 1110-1115, 1935

found tubercle bacilli in the lesions in 3 adults and 3 children These authors were unable to detect any pulmonary changes

The *tuberculin reactions* in children and young adults were positive in over 90 per cent and more strongly positive than in control groups [789] There are series of many hundreds of observations available.[790-796] In a number of instances the test was known to have been negative before the outbreak of erythema nodosum and was observed to become positive [794-795]

The *provocation* of erythema nodosum [840] or at least of n w lesions by tuberculin tests has been reported by Kropatchev and Verzner [841] Wallgren[842] saw erythema nodosum after Calmette-Guérin vaccination Yet it should be emphasized that in large series[792] 3 to 8 per cent of the cases have been definitely declared tuberculin negative

Simultaneous manifestations of tuberculosis have been discovered in many instances Prag[790] saw roentgenologic pulmonary changes in 91 per cent of his 157 cases other authors in about 50 per cent [791,843-846] Few writers found the lungs involved in only a minority of their[847] cases [848]

The pulmonary involvement was usually interpreted as recent or primary [791]

A dense and enlarged hilus tracheobronchial lymphadenopathy peri bronchial infiltration pleural exudate or frank hyperplastic tuberculosis are the usual findings The lymph node enlargement was more often bilateral than uni lateral and the pulmonary infiltration was unilateral in about 50 per cent of the affected cases.[849] The relatively benign character of the hilar reaction is sometimes shown by its complete disappearance in a short time [84]

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[789] Rotnes, P L Erythema Nodosum in the Adult, Nord. med. tidskr 13 281 288 1937 Zbl 61 458.

[790] Prag, A R, Erythema nodosum, Hygiea, Stockholm 94 598-601 1932 Zbl. 44 164

[791] Giertsen C 93 Cases of Erythema Nodosum, Acta med. Scandinav 83: 57 110 1934; Zbl 49: 346

[792] Landorf N Tuberkulinnegatives Erythema nodosum, Acta paediat. 17 160-167 1935 Zbl. 51 268.

[793] Comby J A propos de l érythème noueux. Bull. et mém Soc méd d hôp. de Paris 50 1740-1742 1934 53 975-978 1937

[794] Stavropoulos, J Quelques considérations sur un cas d érythème noueux Bull Soc pédiat. de Paris 33 585-590 1935

[795] Bétboux, L and Berthet E U cas de primo-infection t berculeuse er érythème noueu chez une fillette de onze ans, Bull et mém Soc méd. d hôp de Paris 51 805-810 1935.

[796] Castaneda, L E Rottjer E A and Pasqualini, R Q Erythema Nodosum as Symptom of First Tuberculous Infection in Adults, Rev Asoc méd argent 49 915-922, 1935 Zbl 86 583

[840] Lafosse P Érythème noueux chez une tuberculeuse près des injections de tuberculine Rev de la t ber V 1: 461-462 1935

[841] Kropatchev A N and Verzner V N Erythema Nodosum in Small Children Sovet. pediat. N 12: 57-63, 1936 Zbl 86 59

[842] Wallgren, A Erythema nodosum nach Calmette-Impfung Svens. läk.-tid pp 1307-1295, 1932 Zbl 44 300

[843] Ståhle S Erythema Nodosum Svenska arch sa celok lek 35 146-163 1933 Zbl 45 890

[844] Giertsen C Four Cases of Erythema Nodosum and Frühinfiltrat Acta med Scandinav 83: 58-66, 1934 Zbl 49 347

[845] Hamburg Zetlina, E and Kropatschew A Etiology of Erythema Nodosum in Children Borba tuberk 11 112-115 1931 Zbl 50 6 1

[846] Earl O Beitrag zur Aetiologie des Erythema nodosum, Arch f kinderh 92 295-301 1931.

[847] Paul, L W and Pohle E A Erythema Nodosum, Mediastinal and Pulmonary Changes, Radiology 37 131 137 1941

[848] Spink, W W Pathogenesis of Erythema Nodosum With Special Reference to Tuberculosis, reptococcic Infection and Rheumatic Fever Arch I t. Med 59 65-81 1937

[849] Kerley P The Etiology of Erythema Nodosum, Brit J Radiol. 16 199-204, 1943



Fig. 111 — Erythema nodosum.



Fig. 112 — Erythema nodosum. *Left*, marked enlargement of the mediastinum and hilar lymph nodes. *Right*, four weeks later. There was no demonstrable associated pulmonary disease. (From Poppel and Melamed: New England J. Med.)

The lung changes have quite frequently been interpreted as a primary complex.[884] This is in line with the fact that fresh pulmonary changes are mostly encountered in young individuals It is of special interest that young adults who by their negative tuberculin tests show that they have so far escaped tuberculous infection are more likely to get erythema nodosum on exposure to tuberculous infection than are controls. These persons usually become tuberculin positive in the course of the disease This has been demonstrated in student nurses[[illegible]] and newly inducted soldiers.[[illegible]] Such and similar cases[[illegible]] carry much weight against the argument that a positive tuberculin reaction does not necessarily have to be related to erythema nodosum.[784] If it is true that erythema nodosum is rare in lung sanitariums this could be explained by the fact that most cases in these institutions are no longer in the early stages. Erythema nodosum has been seen to appear in the presence of extrapulmonary tuberculosis e g *a cold abscess of the neck,*[[illegible]] *or of the breast* [[illegible]] *or after the surgical severing of* pleural adhesions.[[illegible]]

Tubercle bacilli in the *blood* of patients with erythema nodosum have been demonstrated quite frequently[[illegible]] (12 5 per cent Saenz and Broca after Milian and Brodier[[illegible]] L. Nékám Jr [[illegible]] *in a case of so-called typhobacillosis*) They do not prove conclusively the tuberculous etiology of the skin lesion since bacillemia is frequent in tuberculosis but they are a valuable support of a hematogenous pathogenesis.

Tubercle bacilli have been demonstrated in the *gastric juice especially of* children with erythema nodosum [[illegible]] and also in the urine (Ramel after Milian and Brodier[[illegible]]) To these findings applies what has been said of the etiologic value of the bacillemia.

[[illegible]]Punch, A L Erythema Nodosum Etiology Lancet 1 10-11 1941

[[illegible]]Tornell, E. Untersuchung von Knotenerythemfällen und ihrer Umgebung in der Fürsorgestelle, [illegible] Nat Tuberk. Kvakr 30 3-12 1935 Zbl [illegible] 178

[[illegible]]Debré, M R Érythème noueux et tuberculose, Bull Soc. franç de dermat et syph 40 II 1091 1096 1933.

[[illegible]]Gordon, H Case of Tuberculous Infection With Erythema Nodosum, Bri J Dermat 45 60-71 1933

[[illegible]]Penny W M Erythema Nodosum, Brit J M [illegible] 140, 1931

[[illegible]]Costa, F and Bernard, J Érythème noueux et néphrit [illegible] section de brides [illegible] tuberculeuse Bull et mém Soc méd d Hôp d Paris 50 1080-1083 1934

[[illegible]]Masstal, R Tuberkelbazillen im Blut bei Erythema nodosum (Negativer Pirquet bei Tuberkulose [illegible] Erythema Nodosum) Verhandl d [illegible] naturf Gesellsch p 442 1933

[[illegible]]Paisseau, G Osmanski V and Duean, F Érythème noueux et tuberculose Bull Soc pédia de Paris 28 [illegible]-458 1930

[[illegible]]Naranjo, F Ueber Tuberkelbacillämie bei Erythema nodosum im Kindesalter Ztschr f. Tuberk 71 11 16, 1934

[[illegible]]Bass, E Erythema Nodosum mit Tuberkelbacillen im Blut. Hospitalstid 76 [illegible] 1933 Zbl 47 [illegible]

[[illegible]]Nékám, J L Fall von Landouzy scher Typhobacillose und Erythema nodosum. Klin. Wchnschr 13 [illegible] 1934

[[illegible]]Goldfel [illegible] A Pathogenese des Erythema nodosum Monatschr f Kinderh 61 [illegible]-267 1935

[[illegible]]Wall [illegible] of Erythema Nodosum [illegible] School Children, Nord med [illegible] [illegible] 453-458 1931 Zbl 40 7 1

[[illegible]]Philli[illegible] of Tubercle Bacilli in the Gastric [illegible] From 100 [illegible] Cases of E[illegible] [illegible] 13 393-395 1932

While the prognosis of the dermatosis itself is good *severe and even fatal tuberculosis* has in a minority of the cases been seen (27 per cent,[illegible] 12 per cent,[illegible] 14 per cent[illegible]) to follow erythema nodosum

Tuberculous meningitis,[illegible] miliary tuberculosis and florid pulmonary phthisis[illegible] have been reported occasionally The most experienced observers agree that every case of erythema nodosum should be watched until the return of normal temperature and normal sedimentation rate

The Scandinavian writers have often emphasized the *public health* aspect of erythema nodosum[illegible] They regard erythema nodosum especially in school children as an indicator of an open source of tuberculosis in the surroundings A school mate[illegible] a family member or a coworker has time and again been found to spread tubercle bacilli which may account for the tuberculous infection by which erythema nodosum seems to be caused After erythema nodosum children should remain in bed for several weeks and should be kept fro school until all danger of acute tuberculosis can be safely disregarded[illegible]

Small *epidemics* of erythema nodosum in hospital wards boarding schools and families[illegible] have been observed several times and the source of the tuberculous infection has often been found[illegible]

After the remarkable evidence which has been produced particularly by the Scandinavian authors it must be accepted that a varying and often large portion of the erythema nodosum eruptions is due to tuberculosis in the early stages particularly in juveniles at the time of the development of skin allergy[illegible] The allergic pathogenesis finds fresh support in the parallel and more clear-cut cases of erythema nodosum in coccidioidomycosis (which see) Here the conditions are less complicated because most of the patients have never been infected and do not come from infected surroundings In coccidioidomycosis the ery

[illegible] Lesné E Boquien, Y and Galliais P Le pronostic éloigné de l érythème noueux, Arch d méd d. enf [illegible] 21-30 19[illegible]

[illegible] Eckerström S Ueber Erythema nodosum and Pleuritis exsudativa in der Krankengeschichte der Lungentuberkulösen, Act [illegible] Scandina [illegible] 1932

[illegible] Stokes, J H Erythema Nodosum and Tuberculosis Arch Derma & Syph 3 [illegible] 1921

[illegible] Moritz D Meningeale Reaktion bei Erythema nodosum, Monatschr f Kinderh 67 [illegible] 1936

[illegible] Chalmers[illegible] T Aetiologie des Erythema nodosum bei Kindern Pediat polska [illegible] 416-420 [illegible] Zbl 44 [illegible]

[illegible] Lesné M E L érythème noueux chez l enfant Bull Soc franç de dermat. et syph. 46 II 1058-1099 1936

[illegible] Ölt che O Eine Erythema nodosum-Endemie in einer Spitalabteilung Monatschr f Kinderh 58 241 259, 1933

[illegible] Eraberg H Das Knotenerythem, ein Warnungssignal, [illegible] Tuberk Kvekr [illegible] 1933 Zbl 51 061

[illegible] Landau, A Multiple [illegible] of Erythema Nodosum [illegible] Class of School Children, Arch Dis Childhood 7 77-82 1932

[illegible] Brandon K F Hardman R P and Birks W H Erythema Nodosum and Tuberculosis, Canad J Pub Health 28 [illegible] 19[illegible]

[illegible] Eraberg H Erythema Nodosum Nord med [illegible] 1932 Zbl 41 717

[illegible] Childs A Tubercular E[illegible] of Erythema Nodosum Rev argent dermatosif, 18 [illegible] 1932 Zbl 41 [illegible]

[illegible] Landau, A Schadepidemie on Erythema nodosum [illegible] pp 1419-1420 1933 Zbl 41 [illegible]

[illegible] Gendron A Érythème noueux et miliaire épidémique Leur apparition fréquente au moment de la primo-infection [illegible] Bull et mém Soc méd d Hôp d Paris 47 [illegible] 1931

[illegible] Lelong M L érythème noueux Faits étiologiques et cliniques Bull Soc franç de dermat. et syph 43 II 1094-100 [illegible]

thema nodosum appears after the primary lung infection has produced allergy The term autogenous tuberculin reaction [339] well expresses the pathogenetic theory Some authors call erythema nodosum the exanthem of tuberculosis. This, too regards the eruption in the light of the general observation that the beginning of the secondary phase of an infectious disease is often marked by an exanthem. The histologic findings sometimes show tuberculoid structure but more often nonspecific inflammation especially around the veins. The lack of eosinophiles is an argument against an allergic pathogenesis.[340] The scarcity or the lack of tubercle bacilli in the lesions cannot be used as an argument against a tuberculous etiology since it may be explained by the strong defense which has developed and for which the positive tuberculin tests are proof While especially in children and in cooler climates the important part which tuberculosis plays seems certain it needs to be emphasized that erythema nodosum has been seen in a great number of other infections [341] e g ulcus molle [347] lymphogranuloma inguinale Boeck s sarcoid coccidioidomycosis, trichophytosis ulcus vulvae acutum (Popoff 1938 after Pautrier[341]) (Samek and Fischer after Pautrier and Woringer[342]) syphilis leprosy measles and rheumatic fever as well as a drug eruption and finally without any apparent cause The knowledge of the varied etiology of erythema nodosum invalidates an argument against a purely tuberculous etiology namely the cases which are numerous in some series in which by no method even by autopsy in some instances could tuberculous infection be found.[339]

The *variations* in the analyses are remarkable Poppel and Melamed[343] found in a New York series only 4 out of 88 cases associated with tuberculosis. Ramel[344] believes that idiopathic erythema nodosum is always, in the child as well as in the adult the cutaneous manifestation of a tuberculous bacillemia It seems best to regard erythema nodosum as a *clinical* rather than an etiological entity however the important role of tuberculosis especially in children cannot be denied

Erythema exudativum multiforme has been suggested to be caused by hematogenous tuberculous infection [344,345] English investigators[346,347] were unable to duplicate the guinea pig inoculations. The idea cannot be considered established except possibly for some cases of the Landouzy type of tuberculous

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[339] Ernberg H Erythema Nodosum and Tuberculosis, Am J Dis Child 46 1307 1307 1933

[340] Grzybowski Erythema Nodosum Bull Soc franç d dermat et syph 45 III 1073-1090 1938

[341] Pautrier L M Ullmo A and Baumeister M P L érythème noueux au cours de diverses infections, Bull Soc franç de dermat et syph 45 II 1307 1225, 1938

[342] Pautrier L M Woringer Fr and Kern, R Érythème papuleux circiné Bull Soc franç de dermat. et syph 40 183-18 1933

[343] Poppel, M H and Melamed, A M Erythema Nodosum, New England J Med 227 325-330, 1942

[344] Ramel, E L éry hème exsuda if multiforme Rapp Congr Dermatologistes Langue franç pp 89-195 1939

[345] Dufourt A Deux cas d typhobacillose ec érythème polymorphe Lyon méd 1930 I 89-92

[346] Percival G H and Gibson H J Etiology of Erythema Exsudativum Multiforme Brit J Dermat 43 329-342 1931

[347] *Hallam, R and Edington J W Investigation of Alleged Tuberculous Etiology of Erythema* Exudativum Multiforme (Hebra) Brit J Derma 45 133-141 1933

bacillemia.[644] Erythema multiforme and other exanthematic erythemas have been seen in association with erythema nodosum (Debré after Milian and Brodier[759])



Fig. 1 3.—Severe, partly bullous erythema exudativum multiforme with typical erythema nodosum on the legs. Tonsillitis acuta polyarthritis. Recurrent attacks in spring.

Initial Exanthems.—In infantile tuberculosis ephemeral and inconspicuous morbilliform roseolar urticarial or erythema multiforme-like exanthems on the arms and legs have been observed occasionally by some authors and quite frequently by others. They may appear at the transition of the pre-allergic into the allergic phase of pulmonary tuberculosis [illegible], i.e. about two months

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[illegible]Senear, F. E. Cutaneous Tuberculosis and General Medical Diagnosis, Ann. Int. Med. 8 1274-1291 1935

[illegible]Uffenheimer, A. Das Erstexanthem (Frühexanthem?) der kindlichen Tuberkuloseinfection München med. Wchnschr. 74 [illegible]-[illegible] 1927

[illegible]von Mériz, D. Tuberculöses Frühexanthem, Wien klin. Wchnschr. 1934 II 1061 1062

[illegible]Kundratitz, K. Das Erstexanthem der kindlichen Tuberkuloseinfektion, Wien. klin. Wchnschr 1928 I 921, 923

after the infection These exanthems being connected with the early allergic phases have been seen mostly in children They are explained along the same lines as erythema nodosum

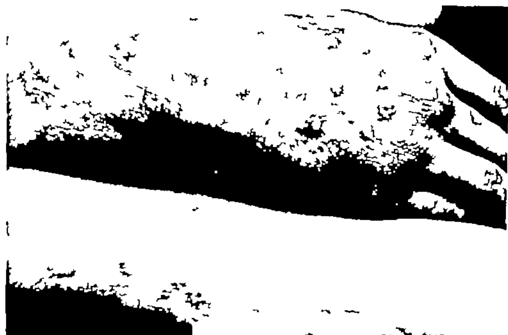


Fig 114 —Erythema exudativum multiforme (Courtesy Dr M Jessner)

Lichen nitidus[illegible] consists of pinhead sized glossy light colored superficial papules which most often occur on the penile skin. The lesions develop slowly and without any characteristic changes. They may stay for years. The microscopic picture is that of an almost too typical tubercle just below the epidermis with many Langhans cells and little necrosis. In a number of cases coincidence with pulmonary or cutaneous tuberculosis has been observed [illegible] but the tuberculous nature of the dermatosis is still controversial

Granuloma annulare (Radcliffe Crocker) is characterized by hard yellow white almost flat papules arranged in coin-sized or larger rings most often on the dorsa of the hands rarely on the arms or elsewhere on the body The course is slow and may become arrested at any stage There are no complications or other changes than spontaneous regression sometimes after many years The microscopic picture shows a deep-seated granuloma with central necrosis rarely[illegible] with a marked tuberculoid structure [illegible]

[illegible] Pinkus F Ueber eine neue knötchenförmige Hauteruption Lichen nitidus Arch f Dermat u Syph 85 11 1907

[illegible] Rasch Granuloma Annulare Zbl 11 401 1921

[illegible] Jacobi F Granuloma Annulare Handb d H u Gk 10, 794-835, 1931

J. Jadassohn[illegible] and later his pupils (Martenstein and Knoll[illegible]) were impressed by the frequently negative tuberculin reactions in granuloma annulare, in spite of many facts which pointed toward a connection with tuberculosis. They felt that granuloma annulare should be grouped with other "positive anergic" tuberculous conditions, especially Boeck's sarcoid. Michael[illegible] reviewed 86 cases from the literature and found a definitely lower percentage of positive reactions than is found in the population at large. Tubercle bacilli have only exceedingly seldom been found in the lesions,[illegible] the guinea pig inoculations being just as unsuccessful as the microscopic examinations. Combinations with pulmonary and other tuberculosis has been seen only in 16 to 20 per cent.[illegible] Tuberculin has had a healing effect in a number of cases and has occasionally provoked lesions.[illegible] The strongest argument against a tuberculous etiology is furnished by a number of cases in early childhood without tuberculosis and with negative tuberculin reactions.[illegible] Granuloma annulare is probably a clinical reaction common to different agents, of which the tubercle bacillus is only one. Some authors believe in a toxic etiology.[illegible]

Boeck's Sarcoid (Benign Miliary Lupoid)

Boeck's sarcoid is a rare systemic disease involving predominantly the skin, the lungs, and the bones.

The trouble usually starts insidiously and takes an extremely chronic and unusually benign course. The original description of Boeck distinguished three types characterized by small disseminated cutaneous nodules or papules, by larger and more grouped nodes, and by diffuse, sometimes very extensive infiltrated plaques. With the greater number of cases published, transitional and other varieties have become known, and cases without skin involvement have been recognized. It is now believed that the skin participates only in about half of the cases (Vosbein and Bonnevie after Leitner[illegible]).

The clinical feature which connects the nodosities of varying size and shape is the diascopic appearance of small yellowish spots which resemble lupus lesions but are smaller and less transparent. These "lupoid" spots, which are responsible for the name benign miliary lupoid, may coalesce into larger areas. The small nodules are usually numerous, giving the impression of an exanthem, while the large nodules occur in smaller numbers. The lesions which are present simultaneously are in various stages of development. In some the skin may still be of normal color, while in others definite lupoid red or brownish discolora-

[illegible] Jadassohn, J.: Sarcoide und Lupus pernio. Kor. Bl. Schweiz. Ärzte 44: 1474-1477, 1914.
[illegible] Michael, J.: Etiology of Granuloma Annulare With Special Reference to the Tuberculous Theory. Arch. Derm. [illegible]
[illegible] Epstein, F.: Relationship of Tuberculosis and Granuloma Annulare. Dermatologica [illegible]
[illegible] F. P.: A Note on the Suggested Tuberculous Origin of Granuloma Annulare. Brit. J. Derma. 41: [illegible] 1929.
[illegible] Kissmeyer, A.: [illegible] étiologie du granuloma annulare. Bull. Soc. franç. de dermat. et syph. [illegible]
[illegible] F. and Ingram, John T.: Granuloma Annulare. Brit. J. Dermat. 47: 219-240, [illegible]
[illegible] Leitner, St.: Der Morbus Besnier-Boeck-Schaumann. Basel, 1942, Benno Schwabe.



Fig. 115.—Boeck sarcoid. Ring-shaped lesion with atrophic center. (Courtesy Division of Dermatology, Department of Medicine, University of Chicago.)



Fig. 116.—Boeck sarcoid. Lupoid appearance under glass pressure. (Courtesy Division of Dermatology, Department of Medicine, University of Chicago.)

tion has already developed. On the face such mature efflorescences are often bluish red with a yellow border.[illegible] Other nodules may be regressing leaving a depressed atrophic scaly scar in the center while the periphery is still active red or brown, sometimes telangiectatic, and infiltrated. Such ring-shaped or circinate figures surrounding a thin scar are particularly characteristic on the forehead and other parts of the face. Other typical though less common sites are the shoulders and the extensor surfaces of the arms, occasionally the hands and feet, where the ring form is usually less marked because the center is more apt to stay pigmented. The scalp may also become affected. Ulceration does not occur.

The *lungs* are frequently affected in Boeck's sarcoid.[illegible] The sarcoid lesions in the lungs are small and disseminated mainly over the middle and lower parts. A diffuse fibrosis with stringy, rather dense shadows radiating from the hilus toward the periphery[illegible] is often noticeable. A diagnosis of Boeck's sarcoid based on the lung picture alone is hardly possible. In cases without skin lesions a diagnosis of miliary or fibrotic tuberculosis, of carcinomatosis or of less specific changes will probably be considered. A characteristic of the pulmonary changes is the chronic course and the fibrotic tendency which is the analogy of the scarring of the skin lesions. In spite of widespread and dense changes of the lungs the symptoms are usually only slight.

This is also true of the *bone* involvement.[illegible] Nielsen[illegible] has observed fifty cases of Boeck's sarcoid over many years. He and many other authors found the small bones, especially the terminal phalanges, most commonly affected. Sarcoid paronychia may precede the bone disease.[illegible] The course is chronic and complete regression of lesions could be demonstrated. The lesions are small round embolic foci of granulation tissue which replace the bone and cause a cyst-like X-ray picture. Pathological fractures occur occasionally. If the bone is heavily affected the surrounding soft tissues may become swollen and produce the picture of dactylitis or spina ventosa. Bone lesions occasionally [illegible] dermoid ones occur in about 20 per cent of the cases.[illegible] Similar bone changes

[illegible] Boeck, [illegible]: Multiple Benign Sarcoid of the Skin, J. Cutan. & Genito-Urin. Dis. [illegible]
[illegible] Schaumann, [illegible]: Boeck's Disease, Acta radiol. [illegible] 1932 [illegible]
[illegible] [illegible]: [illegible] benigna, Nord. med. tidskr. [illegible]
[illegible] Kuznitzky, E., and Bittorf, A.: Boeck'sches Sarkoid mit Beteiligung innerer Organe, [illegible] med. Wchnschr. [illegible]
[illegible] Frank, [illegible]: Boeck's Sarkoid, Lupus pernio und Lymphogranulomatose, [illegible]
[illegible] Nielsen, [illegible]: Recherches radiologiques sur les lésions des os et des poumons dans la maladie de Boeck, Bull. Soc. franç. de dermat. et syph. [illegible] 1934.
[illegible] [illegible]: [illegible] [illegible]
[illegible] [illegible]: [illegible]
[illegible] [illegible] [illegible] multiplex cystica mit Parkinson und [illegible] Jahrb. f. Kinderh. [illegible]
[illegible] [illegible] [illegible]
[illegible] [illegible], [illegible] Paul, [illegible] and [illegible]: [illegible] cystoïdes multiples [illegible] maladie de Perthes-Jüngling [illegible] Bull. Soc. franç. de dermat. et syph. [illegible]

have been seen in some instances of lupus vulgaris (F Koch[873]) The different appearance of tuberculosis of the bones is emphasized by Naegeli [874]

Lymphadenopathy is a common feature. The peripheral as well as the visceral lymph nodes especially those at the hilus are frequently enlarged Schaumann[illegible] found specific sarcoid tissue in the tonsils in all of his cases, and there is enough autoptic evidence that practically all organs may become the site of hematogenous metastases [illegible] Marked monocytosis sometimes as high as 40 per cent is a frequent though not invariable sign which Pinner[illegible] believes to be the hematological manifestation of a monocytic proliferation which also leads to the epithelioid granulomata

It seems that sarcoid is relatively frequent in the American Negro [875]



Fig 117 —Boeck's sarcoid (Courtesy Dr M Jessner)

The *microscopic* structure of the lesions is better characterized by the term noncaseating tuberculosis[illegible] than by the rather vague word sarcoid Dense foci of epithelioid cell tubercles are separated by areas of connective tissue. There is no caseation and little or no lymphocytic infiltration surrounding the lesions so that the apt term naked tubercle has been used Giant cells may be found

[873] Koch F Ortliche Tuberculosis multiplex cystoides (Jüngling) bei Lupus vulgaris, Dermat Wchnschr 1935 101 919-921

[874] Naegeli So les altérations osseuses dans la maladie de Besnier Boeck, Bull Soc franç de dermat et syph 41 1519-1526 1934

[875] Nogland, R Hematogenous Cutaneous Tuberculosis (Sarcoid) in Negroes, Arch. Dermat. & Syph. 30 59-75 1934

According to Pinner tubercle bacilli have been found in the lesions 25 times. This is a small percentage but considering the law of Jadassohn and Lewandowsky the scarcity of microorganisms must be expected in tuberculoid structures and cannot be interpreted against the etiology in question The fact that in a considerable number of instances tubercle bacilli have been demon

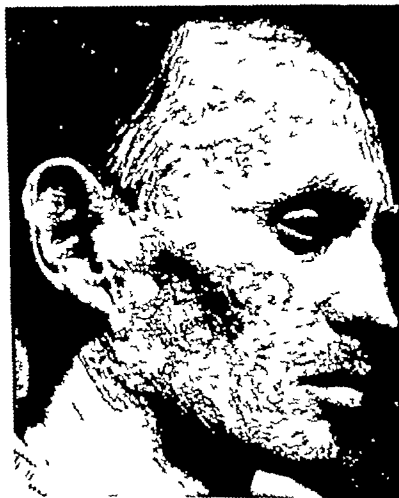


Fig 1 Boeck sarcoid courtesy Dr M Jessner

strated in the lesions is a good argument for the tuberculous etiology of Boeck s sarcoid Kyrle showed that during the first days of a crop of typical Boeck s sarcoid tubercle bacilli were numerous in the still erythematous lesions There were perivascular foci of nonspecific inflammation Around the eleventh day the acid fast bacilli become so[illegible]e and epithelioid cells begin to group together

Kyrle Die A[illegible] des Boeck schen Lupoids Beitrag zur Frage der Uberleitung Aetiologie dieser Dermatose Arch f Derma Syph 131 23-43, 1921

On the thirty-sixth day the typical sarcoid structure with epithelioid cell tubercles and giant cells was fully developed but no bacilli could be found In the early stages the blood too contained tubercle bacilli[877] (see also Leitner[881])

The tuberculin reaction is negative often even to 1 mg of tuberculin or only slightly positive in the great majority of the cases. This *anergy* is much too frequent to be explained by freedom of tuberculous infection Negative tuberculin reactions have even been found in cases of Boeck s sarcoid with frank tuberculosis.[773, 774, 877-87] Zieler[773] however observed that the tuberculin reaction which had been negative in a case of lupus pernio became positive with the



Fig 119 —Boeck sarcoid (Courtesy Dr M Jessner)

outbreak of pulmonary tuberculosis. Lupus pernio is closely related to Boeck s sarcoid Pinner[784] call anergy an essential feature of the disease Reactivity inhibiting substances in the serum so-called anticutins could be demonstrated in four out of eleven patients with sarcoidosis which is less often than anergy[773] but probably more frequent than in normal or tuberculous patients In several animals e g rats dogs cats foxes and horses tuberculosis takes much more often than in man a sarcoid like course with epithelioid cell tubercles absence

[877] Martenstein H Sarkoid Boeck und Lupus pernio Arch f Dermat Syph 147 70 1924

[881] Jadassohn W L origine tuberculeuse d la maladie d Boeck, Bull Soc franç de dermat et syph, 41 1344-1347 1934.

of caseation anergy and anticutins in the serum. This fact furnishes a parallel which can also be used in favor of a tuberculous character of Boeck s sarcoid[875] Finally combination with and transition into frank tuberculosis has frequently been observed. St Epstein[796] found progressive pulmonary tuberculosis in about 12 per cent and less active forms in a still higher percentage[877] sometimes with disappearance of the sarcoid lesions Appearance of the first lesion at the site of trauma[878-880] does not necessarily mean ectogenous infection since the trauma may lower the local resistance and attract the bacteria from the bloodstream In this connection it may be mentioned that subcutaneous injections of many



Fig 120 —Boeck sarcoid (Courtesy Dr Melamed)

substances especially oils may cause reactive changes of great similarity to sarcoid. The majority of the authors now seem to favor a tuberculous etiology of Boeck s sarcoid while dissenting writers, among them Kissmeyer[880] who has wide experience with this rather rare disease hold that the disorder is a specific nosological and etiological entity Kissmeyer[881] bases his opinion on the too rare and in his opinion not always valid findings of acid-fast bacilli on the

[877] Ronchese F Sarcoid and Tuberculosis—Case With Autopsy Arch Dermat. & Syph. 48 860-871 943

[878] Forrester H R and Wieder L M Sarcoid (Boeck Type) Arch Dermat. & Syph. 22: 843 1930

[879] Gougerot H and Blum, P Tuberculose sarcoïde hypodermique par corps étrangers à la suite d' injections de vaccins abcès[illegible] en excipient aqueux, Bull Soc franç. de dermat. et syph. 39: 1834-1837 932

[880] Kissmeyer A Contribution à l'[illegible] de clinique des sarcoïdes, Bull. Soc. franç. de dermat. et syph 41 1103-1107 1934

[881] Kissmeyer A Beitrag zur Aetiologie und Klinik des Boeckschen Sarkoids, Hospitalstid. 1932 II 1047 1079 Zbl 44 837

benign course on a refutation of J Jadassohn's theory of positive anergy and other reasons.* Some writers believe that the disease has the characteristics of a chronic bacillary granuloma with features relating it to tuberculosis syphilis and also to leprosy [illegible] while Rabello Jr [illegible] thinks that tuberculosis, leprosy and perhaps still another disease may produce Boeck's sarcoid Arsenic has a distinct therapeutic influence This fact has been used as an argument against the tuberculous etiology

Lupus Pernio.—Lupus pernio is closely related to Boeck's sarcoid [illegible] It manifests itself as ill-defined cyanotic, cutaneous and subcutaneous nonulcerative plaques most frequently found on the nose and cheeks with marked symmetric tendency On glass pressure lupus-like spots can be demonstrated This rare and chronic disorder affects mostly adults and is combined with bone alterations which resemble those found in Boeck's sarcoid Histology and marked positive anergy to tuberculin are further links to that disease and thus to tuberculosis.[illegible]

Erythrodermia Exfoliativa (Pityriasis Rubra of Hebra)—Universal redness infiltration and scaling accompanied by lymphadenopathy may be a phase in many diseases e.g leukemia arsenic poisoning psoriasis eczema and many others. Jadassohn [887] in an analysis of 18 cases revealed that in at least eight pulmonary and other forms of active tuberculosis were present. Since then many such cases have been described [888]

Purpura Hemorrhagica—The whole syndrome of hemorrhagic purpura, even purpura fulminans (Gaede et al [889]) may be produced by tuberculous infection Miliary tuberculosis of the spleen seems to be especially predisposing particularly in children [illegible] Cases with a fulminating course of less than one day have been observed The number of cases of mild and severe purpura occurring in many types of visceral tuberculosis is considerable so that coincidence is unlikely Some purpuric spots could be shown to possess tubercular structure [illegible] This corresponds to experiences with other purpuric infectious efflorescences e.g the rickettsioses and bacterial meningitis. An old report of a finding of tubercle bacilli in purpuric skin lesions (Beirnende and River 1906 after Volk[illegible]) does not seem to have been confirmed more recently

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*Similarly Leitner[illegible] in recent review interprets the negative tuberculin reactions against t ber culous etiology H also questions he validit of some of he positive findings of bercle bacilli

[884] Kissmeyer A La maladie d Boeck Sarcoïdes cutanées b ignes multiples, Préface de J Darier Paris, 1932, Masson & Cie

[885] Rabello J E Données nouvelles pour l interprétation de l affection de Besnier Boeck rôle de la lèpre A d dermat et syph 7 571-597 1936

[886] Kobayashi E Lupus pernio mit Knochenveränderungen, Jap J Dermat & Urol 31 1569-1573 Zbl 41 1 3

[887] Jadassohn J Pityriasis rubra Hebra und ihre Beziehungen zur Tuberkulose, Arch f Derma Syph 23 911 1891 24 85 273 463 1892

[888] Darney R F Pityriasis Rubra Hebra) Arch Derma & Syph 18 716-729 1928.

[889] Gaede M H nd Vaughn, J) Miliary Tuberculosis With Purpura in Infancy Am J Dis Child 42: 669-673 1931

[890] Quick A J The Hemorrhagic Diseases nd the Physiology of Hemostasis, Springfield Ill 1942 Charles C Thomas

[891] Weiner J J and Carter R F Acut Thrombocytopenic Purpura H morrhagica Associ ed With Tuberculosis (Miliary) of plees pleenectom Wi h Recovery An Surg 113 57-61 1941

Scrofulosis (Scrofula)—Scrofulosis is a syndrome of nontuberculous inflammatory alterations in a child with tuberculosis predominantly of the lymphatic nodes of the neck and of the bones.[illegible] The characteristic combination of swollen or abscessed submaxillary or cervical lymph nodes, eczema especially



Fig. 1 1 Erythroderma pityriasis rubra (Courtesy Dr M Jenner)

around the mouth, blepharitis, phlyctenules, conjunctivitis, otitis media and rhinitis used to be a most common sight in the pediatric clinics of Europe. Scrofulosis is today rare in America[illegible] and has also decreased in other countries. Landis[illegible] believes that scrofula is an infection with the bovine type of the tubercle bacillus. He explains the disappearance of scrofula with the pasteurization of milk. The tuberculin reactions in scrofulous children are strongly positive.

[illegible] n Tuberculosis—Human infections with tuberculosis of birds, usually chickens, may lead to severe systemic and cutaneous diseases which have re-

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[illegible] Marfan, A. B.: La scrofule: conception ancienne, conception nouvelle, Paris méd. 11: 13-20, [illegible]

[illegible] Landis, H. R. M.: The Disappearance of Scrofula, Am. Rev. Tuberc. 21: [illegible]-201, 1930.

semblance to all known types of human tuberculosis but do not quite fit into the familiar pictures. Thus aphthous and septicemic, sarcoid, gummatous and ulcerative forms have been described.[393, 394-396]

The diagnosis will rest on the chicken experiment, the positive avian tuberculin test and the bacteriological culture. The cases seem to be rare. However the diagnosis is important since specific tuberculin treatment has been effective in the cure of such patients (Löwenstein and Joannovic quoted by Urbach[394]).

Lupus Erythematosus Chronicus

The term lupus erythematosus (érythemateux) was coined in 1851 by Cazenave in a clear differentiation from other forms of lupus, as many destructive dermatoses were called. Cazenave (after the French text given by Paul Richter[397]) describes this form of lupus as one which destroys superficially and which does not develop tubercles (which in Cazenave's time meant ulcerating nodules). The relationship of the disease which we now call lupus vulgaris to tuberculosis was then, of course, not yet understood, because our present conception of tuberculosis, which is based on the presence of the tubercle bacillus or its derivatives, did not yet exist. In 1884 Robert Koch demonstrated by culture and animal experiment the tubercle bacillus in lupus vulgaris. After Koch the term lupus became definitely associated with tuberculosis. Despite the fact that Koch dealt



Fig. 122.—Lupus erythematosus discoides.

[394] Urbach, F. Das Krankheitsbild der Geflügeltuberkulose der Haut beim Menschen und beim Tier. Arch. f. Dermat. u. Syph. 157: 260-271, 1929.
[395] Löwenstein, E. Das Krankheitsbild der Hühnertuberkulose beim Menschen. Schweiz. med. Wchnschr. 2: 605-610, 1931.
[396] Keri, W. Geflügeltuberkulose. Verhandl. 9. Internat. Kong. Derm. 2: 269-273, 1936.
[397] Richter, P. Geschichte der Dermatologie. Handb. d. H. u. Gk. 14, 2: 206, 1928.

with lupus vulgaris only his work had the effect of stimulating research to prove the hypothesis of a tuberculous nature of lupus erythematosus also

The French dermatologists under Besnier's influence generally adopted the tuberculous etiology of lupus erythematosus while the majority of the German authors concerned with the question rejected this theory for a long time. Later on the Germans gradually and very reluctantly became more inclined to acknowledge the importance of tuberculosis in the etiology of lupus erythematosus.



Fig 123 – Lupus erythematosus chronicus

In the lesions of lupus erythematosus the *tubercle bacillus* has rarely been demonstrated with the Ziehl-Neelsen stain [739, 833] In several instances acid fast bacilli closely resembling the tubercle bacillus have been found in the sediment from tissues destroyed with antiformin. The etiologic significance of these findings must be considered doubtful because such para tubercle bacilli have been found in many media and the antiformin method does not permit the differentiation of bacilli originating from the surface from those from the depth. In spite of negative control tests in normal skin[833] these antiformin findings have not been acknowledged as an etiologic proof [736, 833]

As far back as 1906 Gougerot succeeded in demonstrating the presence of the tubercle bacillus in the lesions of lupus erythematosus by means of animal inoculation These findings have been confirmed several times[739, 740] though a great

[736]Friedländer D The Etiology of Lupus Erythematodes Special Reference to Tuberculosis, J Cutan & Genito-Urin Dis 29: 417 1911

[739]Veiel, F Lupus erythematodes (Caseate) Handb d H Gk 10 1 647 794, 1931

[740]Bloch, Br and Fuchs, H Chronic Lupus Erythematodes and Tuberculosis, Arch f Dermat. Syph 116 742 1913

semblance to all known types of human tuberculosis but do not quite fit into the familiar pictures Thus aphthous and septicemic sarcoid gummatous and ulcerative forms have been described [394, 394-396]

The diagnosis will rest on the chicken experiment the positive avian tuberculin test and the bacteriological culture The cases seem to be rare However the diagnosis is important since specific tuberculin treatment has been effective in the cure of such patients (Löwenstein and Joannovic quoted by Urbach[394])

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ter[397]) describes this form of lupus as one which destroys superficially and which does not develop tubercles (which in Cazenave's time meant ulcerating nodules) The relationship of the disease which we now call lupus vulgaris to tuberculosis was then of course not yet understood because our present conception of tuberculosis which is based on the presence of the tubercle bacillus or its derivatives did not yet exist In 1884 Robert Koch demonstrated by culture and animal experiment the tubercle bacillus in lupus vulgaris. After Koch the term lupus became definitely associated with tuberculosis Despite the fact that Koch dealt

[394]Urbach, E Das Krankheitsbild der Geflügeltuberkulose der Haut beim Menschen und beim Tier Arch f Derm Syph 157 360-38 1929

[395]Löwenstein, E Das Krankheitsbild der Hühnertuberkulose beim Menschen, Schweiz med Wchnschr 2 609-610 1931

[396]Kerl W Geflügeltuberkulose Verhandl 9 In ernat Kong. Derm 2 260-272 1936

[397]Richter P Geschicht der Dermatologie Handb f H u. Gk. 14, 2 206 1928

observations carry as little weight in the discussion of the tuberculous etiology of lupus erythematosus as the successful treatment with tuberculin One should also remember that nonspecific focal reactions have been seen after injections of many substances, e.g gold milk and other foreign proteins sulphur etc.

It is important in the discussion of the tuberculous origin of lupus erythematosus to consider whether or not this condition is *more frequently found in tuberculous than in nontuberculous* individuals The opinions on this are extremely contradictory Goeckerman[illegible] denies that lupus erythematosus is substantially more frequently associated with tuberculosis (36 per cent) than other dermatoses (32 per cent) The number of authors who believe that lupus erythematosus is a disease of persons with tuberculosis especially pulmonary and glandular is large Ehrmann and Falkenstein[illegible] claim that tuberculosis could be demonstrated in about 50 per cent of the acute cases of lupus erythematosus in about 80 per cent of the chronic cases of lupus erythematosus with acute exacerbation and in 98 per cent of chronic lupus erythematosus. Oros's[illegible] figures run similarly high Pautrier and Schaaff[illegible] give 72 per cent The most recent survey is that of St Epstein[illegible] who examined 200 cases of lupus erythematosus in 7 2 per cent of which active tuberculosis of the lungs could be demonstrated by X ray This is much less than in cutaneous tuberculosis (16 1 per cent) but much higher than in the controls (3 7 per cent) which were taken of the syphilitic patients in the hospital

On the other hand in a great number of cases it has been impossible to produce any evidence of tuberculosis either during life or post mortem Of course the value of such negative findings is always limited because small foci can easily be overlooked The complement fixation tests with the antigens of Besredka Calmette Ponndorf and others did not corroborate the tuberculous origin of lupus erythematosus.[illegible] *Combination with skin tuberculosis* such as lupus vulgaris scrofuloderma or the so-called tuberculids has quite often been reported Lewandowsky[illegible] wrote in 1916 that the reports about the combination of lupus erythematosus and tuberculids had lately become too numerous to be explained by coincidence Since then these reports have multiplied Practically every type of skin tuberculosis has been seen in combination with lupus erythematosus. Lupus erythematosus as well as skin tuberculosis being rare diseases, the number of reported combinations seem to exceed by far the rate of pure coincidence Urbach[illegible] saw lesions of lupus erythematosus the diagnosis of which he secured by histological examination develop in the neigh

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Goeckerman W H I Lupus Erythematosus discoides chronicus due to Tuberculosis? Arch. Dermat & Syph 8 765-80 1921

Ehrmann and Falkenstein F Lupus erythematodes, Arch f Derm Syph 141 408 1922

Pautrier L M and Schaaff Results of Systematic X-ray Examination of Lungs in 29 Cases of Lupus Erythematosus, Ibid
[illegible]

Silberbmann K Komplementbindungsreaktion bei der Tuberkulose mit besonderer Berücksichtigung der [illegible] Die Komplementbindungsreaktion bei Lupus erythematodes, Acta dermat venereol 7 3 [illegible]

Urbach E Lupus erythematodes in der [illegible] Umgebung eines [illegible] Skrofuloderma, Ibid, 11 [illegible] 1924

borhood of a tuberculous fistula. Stühmer[919] saw true lupus nodules in the scar of lupus erythematosus. The rarity of such observations in America may be explained by the fact that cases of skin tuberculosis are only about one-tenth as frequent in North America as they are in Central Europe. As mentioned before lupus erythematosus is about as common in America as it is in Europe. This lack of parallelism seems to indicate that lupus erythematosus, in spite of many relations to tuberculosis is governed by another law than true tuberculosis of the skin.

Without going into detail it may be mentioned that evidence of similar character as that in favor of a tuberculous etiology has been produced in support of other bacteria syphilis mechanical trauma cold light and other agents.

Thus in spite of the great efforts which have been made the role of tuberculosis in the etiology of lupus erythematosus chronicus *remains controversial*.

Lupus Erythematosus Acutus

The most important systemic relationship of lupus erythematosus exists in the rare cases in which the dermatosis either starts with an acute dissemination or where an apparently chronic lupus erythematosus changes its character and becomes *acute* (*Lupus erythematosus acutus and lupus erythematosus chronicus cum exacerbatione acuta*).

Transitional cases between all types of lupus erythematosus have been demonstrated. They prove the close relationship of the various types.

The acute form of lupus erythematosus seems to occur *in all ages* but the majority of the patients are those in the third and fourth decade.

The *sex* distribution of the acute forms has the ratio of three females to one male. This ratio is based on a review of 100 cases published in the last twenty years.

Many factors can change the character of chronic lupus erythematosus into the acute form. Known to have provoked acute lupus erythematosus are exposure to sun and to strong artificial light[920-922] bee stings applied for the treatment of arthritis[923] mosquito bites gold therapy trivial infections like otitis media[924] or such following tooth extraction[925] lymphangitis[922] polyarthritis[926] and physical and mental strain[927]. In many cases however the disease apparently begins without any such factors.

[919]Various authors Lupus erythematosus Symposium on Arguments For and Against Tuberculous Nature, Dermat Wchnschr 99 1346-1356 1934

[920]Roxburgh, A C Acute Disseminated Lupus Erythematosus Five Fatal Cases, Brit. J Dermat 45 85-100 1933

[921]H [illegible] Lupus erythematodes, Zbl 17 268, 1935.

[922]Hess, J H Generalized Lupus Erythematosus and Intra-abdominal Tumor Am J Dis Child 28 129-13[illegible] 1924

[923]Gross O Beiträge zur Klinik und Histologie des Lupus erythematosus acutus, Arch. f Dermat 8 ph 147 424-436 1924

[924]Vail, [illegible] Pathogenese und pathologische Anatomie des Lupus erythematodes acutus, Moskov med. Z [illegible] Zbl 36 125 193[illegible]

[925]Clark F B and Warnock, A W Lupus Erythematosus Acutus Disseminatus, California & West Med 24 334-337 1926

[926]*Gibson R F A Case of Lupus Erythematosus*, With Post Mortem, Brit J Dermat. 37 232 1925

[927]Eastman M F J Early Acute Lupus Erythematosus Arch. Dermat. & Syph 35 [illegible] 1937



Fig 121.—Lupus erythematosus acutus (Courtesy Dr M Jessner)



Fig. 123. Subacute lupus erythematosus nephritis Exacerbation after prolonged exposure to sunlight early in spring.

The *onset* may be sudden with chills high temperature and all the symptoms of an acute infection However there are cases starting with relatively mild attacks of skin eruptions even without fever Excessive fatigue is an outstanding complaint.

The most constant early cutaneous lesion is the appearance of sharply outlined red patches on the face These *erythemas* are often arranged in butterfly or bat shape covering the nose and the malar prominences the ears especially the upper parts of the helix the chin and the neck. Here the erythema is often limited to the lower anterior part the neck V which particularly in women is exposed to the light. The erythema is often but not always edematous or vesiculous especially in severe cases. The rash can simulate erysipelas but the symmetry the development from a number of small individual erythematous lesions the comparative stability and the course will soon differentiate the two In the edema the follicles appear more open creating an orange-peel like surface



Fig. 130 Lupus erythematosus, acute dissemination after first prolonged exposure t sun l spring Scalp lesion ith loss of hair and [illegible] open follicles

The simultaneous appearance of lesions of the scalp and fingers is very characteristic The so-called erythema perstans of the face may remain throughout the whole course of the disease It may disappear and recur The erythematous eruptions may spread over large areas even over the whole body surface. Exudative features like vesicles blisters and crusts sometimes create an eczematous impetiginous or even pemphigoid appearance Hemorrhagic lesions mostly of small size have often been observed

In some cases the skin lesions have a more exanthem like appearance described a a roseola or as a morbilliform rash Often the skin lesions appear in crops which fade or heal and recur often after intervals of indefinite length It is a definite characteristic of the dermatosis to center" about the nose and neck. Here the lesions are redder more deeply infiltrated more constantly observed and healing with atrophy i more frequent than in other sites [14] More or less acute oral and tonsillar infection are not uncommon

In acute lupus erythematosus the cutaneous eruption is *not* the most important part of the picture. It is the syndrome of a severe systemic infection or todc reaction which determines the picture and the course. Continuous high fever is an almost regular symptom. General malaise and later on prostration and exhaustion are frequent.



Fig. 127. Fig. 128. Fig. 129.

Fig. 127. — Lupus erythematosus acutus. (Patient of Dr. S. Rosenthal.)

Fig. 128. Lupus erythematosus acutus. Detail of face. Note open follicles. (Patient of Dr. S. Rosenthal.)

Fig. 129. Lupus erythematosus acutus. Effluvium capillorum during prolonged febrile disease. (Patient of Dr. S. Rosenthal.)

Lymphadenitis, arthritis and more often arthralgia without true arthritis are other septic symptoms. The joint pains frequently accompany the acute exacerbations. The spleen is often enlarged.

Nephritis often with a high albumin content of the urine is one of the most constant and often early complications. Retinitis albuminurica has been seen several times. *Hematoporphyrin* in the urine is a frequent finding in acute lupus erythematosus especially in the severe cases. The photosensitizing effect of hematoporphyrin is well established[illegible] *Colitis* and *enteritis* often not only cause diarrhea but severe abdominal pain which has caused unnecessary appendectomies in several instances.[illegible] *Endocarditis myocarditis* and *bronchopneumonia* are common and together with renal failure frequently the immediate cause of death



Fig [illegible] Lupus erythematosus acut [illegible] Neck [illegible] rash in neck [illegible] area. Courtesy D M Jeamer)

The *blood cultures* done in a great number of cases of acute lupus erythematosus have usually been negative Occasionally streptococci were found[illegible] and very rarely staphylococci and bacterium coli These and some other findings probably are terminal or incidental The largely negative blood cultures indicate toxemia rather than bacteremia

Leukocytosis of 15 20 000 or more has been observed several times but it is the exception Much mor frequently the *white count is low* even as extremely low as 800 It has been emphasized[illegible] that even complications like pneumonia pleurisy nephritis and endocarditis failed to raise the low white count. The

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[illegible] Derlag F and Darzewska, J Aktinische Dermatosen Handb d H [illegible] Ok 4 1 [illegible] 1932

[illegible] Rose E and Goldberg L Lupus Erythema [illegible] Visceral Lesions of [illegible] Dermatos of Lupus, M Clin North America 19 [illegible] 935

[illegible] Ostrowski Lupus erythemat odes acutus [illegible] 21 139 1927

[illegible] Kleissel H W Zur Klinik ud Aetiologie des Lupus erythemat odes acu München med Wchnschr 72 1023 [illegible] 1925

[illegible] Wendt H Lupus Erythema [illegible] Int real Disease München med Wchnschr 81 217 193[illegible]

granulocytes are the elements which suffer most while the lymphocytes prove to be more resistant so that a relative lymphocytosis may result. Aneosinophilia is another frequent and unfavorable occurrence. The reappearance of the eosinophiles often accompanies improvement and remissions. Purpuric spots, petechial showers and thrombocytopenia are recognized features of the syndrome.[[illegible]] Wendt emphasizes that his patients with leukopenia, thrombopenia and purpura had not received gold treatment, which can cause similar lesions.

Secondary *anemia* is frequent. The sedimentation rate is often increased.



Fig. 131. Petechia in lupus erythematosus acutus.

Acute lupus erythematosus is a very dangerous disease in both its forms though the acute exacerbation of a pre-existing chronic discoid lupus erythematosus has a better chance to heal or to return to the chronic stage than have the primarily acute cases.[[illegible]] Out of 100 cases published from 1920 to 1940 at least 76 ended fatally. Recovery being rare, only a few cases of the transition of true acute lupus erythematosus into the chronic discoid form have been observed.[[illegible]]

The gross pathologic findings consist of a variety of septic, renal, pulmonary and liver changes, splenic infarcts and muscular and valvular heart lesions.[[illegible]]

In 111 autopsies in acute lupus erythematosus (Gawalovski[[illegible]]) tuberculosis was the sole finding in somewhat more than 50 per cent. In less than 50 per cent there were no traces of tuberculosis, but usually another bacterial infection was present. Other experiences were similar.

[[illegible]] Rose, E. and Pillsbury, D. M.: Acute Disseminated Lupus Erythematosus, Systemic Disease, Ann. Int. Med. 12: 951-963, 1939.

[[illegible]] Keil, H.: Lupus Erythematosus and Its Morphologic Variants With Particular Relation to "Systemic" Lupus Erythematosus, Arch. Dermat. & Syph. 36: 729-757, 1937.

[[illegible]] Gulon, C. M. and Adams, E. C.: Six Autopsied Cases of Disseminated Lupus Erythematosus, Am. J. M. Sc. 206: 33, 1943.

[[illegible]] Gawalovski, K.: Lupus erythematosus acutus. Étude critique. Acta dermat.-venereol. 10: 1-39, 1929.

It is likely that the twenty cases of erythema with visceral lesions described by William *Osler*[837] in 1904 included cases of lupus erythematosus acutus. The outstanding lesions were purpura erythema colic nephritis and arthritis There is little clinical or post mortem evidence of endocarditis

The *Libman-Sacks syndrome*[838, 839] consists of a peculiar verrucous endocarditis differing from that in rheumatic fever mainly by the absence of Aschoff bodies. The patients are mostly young females Six out of eleven had lupus *erythematosus three more only erythema.* Purpuric symptoms were common Leukopenia and thrombocytopenia occurred Pericarditis arthritis and nephritis were found in almost every case

It has been pointed out that all the symptoms of lupus erythematosus acutus are rather fluctuating It is likely though not yet certain that the Osler[837] erythema group and the Libman Sacks[838] syndrome and acute lupus erythematosus form an entity which often but not always develops typical dermadromes The fundamental and common pathology of the group can possibly be seen in the widespread vascular lesions of the finer ramifications described by Baehr Klemperer and Schifrin [840] These lesions consisting in capillary dilation endothelial proliferation a peculiar hyaline degeneration thrombosis and extravasation were found in all viscera in about 25 per cent of the cases but they were most frequent in the skin and in the kidneys. Glomerular changes of this kind make the thickened capillary wall appear rigid as if made of heavy wire. These 'wire loop lesions which were present in more than 50 per cent of the cases and which have been often confirmed[839, 841, 842] are very striking The authors emphasize that *they have not seen them in any other human disease except perhaps in eclampsia* Similar lesions were found in horses which had been immunized by frequently repeated intravenous injections of live bacteria especially of the pneumococcus-streptococcus group

More recently[843] a new conception based on observations of physicochemical alterations in the fibers and ground substance of the connective tissue has been developed

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[837] Osler W The Erythema Group of Skin Diseases, Am. J M Sc 127 1 1904

[838] Libman, E and Sacks, B A Hitherto Undescribed Form of Valvular and Mural Endocarditis, Arch I Med. 33 701 1924

[839] Belot G H and Ra[illegible] H S V Lupus Erythematosus—So-called Libman-Sacks-Syndrome—Relation Dermatology Arch Dermat & Syph. 33 642 1936.

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[842] Denzer & Blumenthal Acut Lupus Erythematosus Disseminatus, Am. J Dis Child. 53: 525 1937

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Chapter XII

LEPROSY*

History

Leprosy has been known in the near and far Orient from time immemorial. The Bible is replete with mentionings and ruthless laws of quarantine dealing with a disease called zaraath, literally uncleanliness or contamination in the Hebrew original, and translated by the sages of the Septuaginta with the Greek word lepra. Though there is still some doubt about the identity of zaraath and leprosy, the majority of the medical archeologists believe in it. From the stern biblical law stems the general fear and the cruel treatment of the lepers throughout the Christian era almost up to our times. The numerous lepers of medieval Europe were completely outlawed and excluded from all relations with their fellow men. They lived as beggars, compelled to announce their approach and presence by loud rattles, bells or horns, and to take the alms, on which they existed, in bags on a long stick. It is a great merit of the Christian church to have tried to ease the fate of the lepers in many ways, especially by the foundation of many leprosaria throughout the western world.[illegible]

The modern history of leprosy starts with the discovery of the leprosy bacillus by Armauer Hansen (1873), an accomplishment to which Albert Neisser contributed in many ways.

Geography.—At present the number of lepers in the world amounts to about 3 million. While the majority of them live in the three main centers of Eastern Asia, India and Africa, smaller endemic foci exist in many other countries, mainly the tropics, but also in the United States, the Mediterranean, Norway, the Baltic and Russia. Occasional cases appear in the great centers of immigration and world traffic. In the United States the disease has probably been introduced by Negro slaves and other immigrants. A small epidemic of about one hundred cases was discovered among the Scandinavian immigrants in Minnesota. Leprosy is now to a relatively small extent endemic along the gulf coast. About four hundred lepers, many of them foreign born, live in the modern National

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*Mainly based on the monographs of Lewandowsky,[illegible] Jadassohn,[illegible] Leloir,[illegible] Neisser,[illegible] Schaeffer,[illegible] Klingmüller,[illegible] E. Muir.[illegible]

[illegible] Lewandowsky, F.: Lepra. Handb. d. inn. Medizin, [illegible] 1925.

[illegible] Jadassohn, J.: Lepra. Handb. d. path. Mikroorg. [illegible] 1928.

[illegible] Leloir, H.: Traité [illegible] de la lèpre. Paris, 1886.

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[illegible] Schaeffer, J.: Lepra. [illegible] Leprakonferenz, Berlin, [illegible] Arch. f. Dermat. u. Syph. [illegible]

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[illegible] Muir, E.: Leprosy, Diagnosis, Treatment and Prevention. Ed. [illegible] Delhi and [illegible] India, [illegible] British Empire Leprosy Relief Association.

[illegible] Grön, K.: Die Lepra [illegible] Handb. d. H. u. Gk. [illegible] 1930.

Leprosarium in Carville Louisiana [illegible] Great numbers of lepers live in the Philippines and in Hawaii where under American administration important scientific observations have been made The leper island of Culion in the Philippines and the Kalihi hospital of the United States Public Health Service in Honolulu have in many ways become model institutions Some authors think that leprosy existed in America before the voyage of Columbus.

Etiology Contagion —Leprosy is caused by the Hansen Neisser bacillus, an acid fast rod which in many ways is related to the tubercle bacillus. It stains best with the Ziehl Neelsen method but it is a little stouter and straighter more angular if bent and usually more numerous and more apt to form bundles than the tubercle bacillus

Culture as well as progressive infection of animals, has not yet been accomplished in an entirely satisfactory and corroborated way Though this has hampered elucidation of many phenomena the etiologic role of the Hansen Neisser bacillus has been sufficiently demonstrated by its constant presence in almost all leprous lesions in the blood in the majority of the organs in about 50 per cent of the cases and in all secretions, as well as by its absence in other diseases and in healthy individuals from leprosy free surroundings

Leprosy is a moderately contagious disease The epidemiology is still contradictory Most individuals according to Muir [illegible] nine out of ten seem to possess a high degree of *resistance* This is demonstrated by many instances of *persons who remained healthy in spite of exposure to massive infection over a* long period of time These were mostly family members who lived together with contagious lepers Conjugal leprosy is not common and contagion by intercourse occurs rarely Nurses and physicians caring for lepers have not very often become lepers It is hard to decide how much credit must be given to sanitary measures and avoiding contact.

True congenital leprosy is rare Rodriguez[illegible] did not find a single case in 871 children born of lepers in the Culion colony Many children in leprous surroundings become infected early in life but many stay healthy [illegible] Breast *feeding is not an important factor in the transmission of leprosy from mother to* child [illegible] Contact with contagious lepers in close living quarters seems the main way of transmission but even under such conditions contagion does not invariably occur The author saw a leper covered with tuberous lesions who lived for 16 years in one room with his family all members of which remained healthy

Though experienced leprologists believe that the leprosy bacillus does not live long outside the human body many authors are convinced that the disease can be carried by insects especially bedbugs and acari and a variety of fomites

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[illegible] Hopkins R and Faget G H Recent Trends of Leprosy in the U S A J A M A 126 937 943 1944

[illegible] Muir E Importance of Natural Resistance in Leprosy J Far East A Trop Med 2 [illegible] 547 1932.

[illegible] Muir E Leprosy—Resistance and Typing of the Lesions Leprosy Rev 10 [illegible] 1939

[illegible] Rodriguez J Leprosy [illegible] Philippine J Sc 27 455 1926 31 115, 1926 J Philippine Islands M A 6 40 192[illegible] 6 43 1926 6 358 192[illegible] 6 447 1929 Monthly Bull Philippine Health Serv 8 22 192[illegible] 8 702 1929 6th Congr Far East A Trop Med. Tokyo, 1925, 2 [illegible] 1926.

among which bedding plays a major role Airborne droplets from coughing and sneezing may carry the microbes [H] but the importance of this way of transmission is controversial. The infection of the nose with the fingernails is important Leprosy is mostly a disease of the underprivileged classes intimately connected with dirt poor housing poor diet and other unsanitary conditions.

Incubation General Course, Types.—The incubation period is extremely variable, the observations ranging from one week to as long as 32 years. The average may be one or a few years Rodriguez [###] in observations of children of lepers in Culion found it to be three years nine months. The course of the manifest disease itself is extremely variable with regard to severity of symptoms type of prevailing lesions acute attacks remissions complications and final outcome. In spite of all variations and transitions three definite clinical types stand out

Lepra lepromatosa (tuberous, cutaneous leprosy L type)

Lepra nervosa (anesthetic, neural leprosy N type)

Lepra mixta (L plus N type)

Lepra maculosa is not a type but rather a stage which may be encountered in any of the three types. One or the other type is usually predominant in an area e.g neural leprosy in China. The general rule that the neural type is more common in the tropics and the lepromatous variety in the temperate climates has many exceptions.

The Clinical E pecially Cutaneou Symptoms of Leprosy

The Early Stages. The *primary* skin lesion is a round pink tan copper colored or whitish smooth usually single macula of about 1 cm. which grows slowly up to se eral cent meters in size and may remain stationary over a long time The surf ce is glossy and the edge slightly raised Later when the peri phery grows the center appears depressed or even atrophic. Frequently there is a depigmented areola. *Depigmentation* more pronounced in the colored skin is often the most noticeable element.[###] Sooner or later *nervous* signs and symptoms in the affected area start. A period of hyperesthesia or numbness[###] may precede the anesthesia While the sense of temperature is most often the first to be disturbed after a short time touch and pain and later the sweat secretion become equally impa red The primary lesion is rarely an object of medical attention It is hardly ever seen in the leprosarium in Carville La. (Personal communication to the author) The best observations of initial manifestations were obtained by Rodriguez[###] among the children of lepers in Culion in the Ph l ppines The primary lesions may look very trivial especially in the colored skin which becomes easily dep gmented after scratches and banal pyogenic infection However the detection of anesthesia establishes the diagnosis of leprosy Bacilli are not very numerous in the primary lesions. Rodriguez[###] found that th commonest in tial sites were the buttocks, the cheeks, the posterior nd lateral surfaces of the thighs nd the loins The experiences of other observers are similar [##] The primary lesion was never seen on the chest or the abdomen a frequent site of later lesions.

The primary sore is often found on the *nasal mucosa*. Here it may appear as an ulcer of the anterior septum causing epistaxis which is a well known early symptom. Bacilli may usually be found early in the nasal mucus. Mouth and tonsils are other portals of entry.

Some authors believe that leprosy may develop without a primary lesion. In other cases nervous manifestations may be the first signals of the infection.

Since the primary lesion is frequently inconspicuous and without subjective symptoms the *diagnosis of leprosy is usually made after its generalization* which occurs through the bloodstream and the lymphatics.



Fig. 132 — Leprosy. Early pigmented and depigmented maculae. (Courtesy U. S. Marine Hospital, Carville, La.)

The following types of lesions, any of which may be noticed first, represent the most characteristic elements of *early generalized leprosy*.

1. *Erythematous maculae* of bluish or pinkish hue which in their early stages fade on pressure. The red spots start as small round lesions of less than 1 cm. in diameter but they grow, multiply, coalesce and form gyrate patterns. The later appearing lesions grow quickly. The individual lesion may disappear without any sequelae or may leave the skin pigmented or depigmented. Depigmented areolae and shift of pigmentation make them resemble primary lesions, especially when greater activity causes infiltration. The red spots are found on the face, on the ears, buttocks, the extensor surfaces of the extremities and sometimes on the back. A fine dusty desquamation may be seen on the early maculae.[867]

2. *Pigmented maculae* which may be primary or develop from erythematous macules. At first they look like freckles or chloasma; later they may grow to

[867] Chiyu[illegible] and Velasco, F.: Lepra. Mon. Bull. Philippine Health Serv. 11: 8, 7, 1931.

hand size. Their distribution is that of the red spots. Sometimes they form gyrate or variegated patterns. There is neither infiltration nor desquamation In their usually extremely chronic course they lead to nervous leprosy

3 *Depigmented maculae* (White spots) which have no or only slightly in filtrated edges. They are not completely devoid of pigment but relatively light, especially in the colored skin The earliest white spots are perifollicular with slight follicular keratoses They are 1 to 10 cm. in diameter sometimes numerous and arranged in large network like patterns, thus resembling tinea versicolor or vitiligo Vitiligo however has more distinct borders and the depigmentation is more pronounced Sooner or later anesthesia loss of hair anidrosis and other symptoms of nervous leprosy become manifest. The lesions may acquire an infiltrated active margin Sometimes they become the site of vesicles or bullae. They may heal with scars.

4 *Local swellings infiltrations and nodules* in early leprosy are often first noticed on the alae nasi the ear lobes the elbows and the knees. They usually develop in or close to the red spots and may become large plaques They may be few in number or abundant. The cutaneous nodules vary from pinhead to walnut size. At first the surface is greasy and smooth later dry and scaly resembling psoriasis. They often appear in crops accompanied by fever and other general symptoms. They grow fast but their growth may become arrested in any stage and there may be no change for years. New nodules may appear around the old ones which may heal with a scar Some nodules or deep painful *ulcers* especially under unsanitary conditions occur on the exposed areas of the skin The ulcers may destroy tendons and muscle and the scars may lead to serious contractures and deformities and to strictures of the upper air passages.

Anesthesia at first only for heat and pain later for touch is common in the nodules. The bacilli are numerous.

5 *Blisters* and bullae of all sizes may appear on white or red macules or on the normal skin and may form torpid ulcers The blisters are rare as early symptoms. Early microvesicular eruptions which microscopically proved to be lepra were seen in the Philippines in 16 of 40 children [897]

6 *Nervous disorders* especially disturbances of sensitivity may occur early and are *not restricted to the visible lesions* Numbness, a leather glove feeling itching and other *paresthesias* especially along the extremities, may become very annoying [898] *Hyperesthesia* may make the patients move slowly to avoid any touch They may be unable to turn a key because the pressure of the key against the fingers causes severe pain This phenomenon has been called the sign of the key by a leprous doctor who discovered it in himself

Pain on percussion of the bones, especially the clavicles the olecranon and the skull is often early and pronounced The deep structures of the foot may be very painful on extension of the ankle joint.

Anesthesia a most important sign may develop in connection with visible lesions or independently in apparently normal skin Rodriguez[899] found leprous anesthesia fickle and variable and he failed to find anesthesia in cutaneous lesions in 16 per cent of the cases. The legs, dorsa of the feet forearms, hands and

fingers in the order named are the most frequent sites of anesthesia [illegible] Frazier[illegible] emphasizes the peculiar dissociation of the elements of sensation The perception of temperature disappears first. Then follows anesthesia for pain and finally for touch [illegible] Anesthesia of the little finger especially of the left little finger has often been mentioned as an early symptom Early anesthetic areas are often found on the ulnar aspects of the forearms and hands and on the lateral surfaces of the lower legs and feet. The nervous disorder may appear on all kinds of macules and trophic ulcers may develop in all anesthetic areas. The superficial nerves most often the ulnar nerve the peroneal and the auricularis magnus may early become thickened and palpable. Atrophy of the musculi interossei and of the hypothenar eminences are further early nervous symptoms.

7 *Anidrosis* especially of the finger tips is an early symptom and may precede anesthesia. Some disturbance of the sweat secretion can be demonstrated in 70 per cent of the cases (Degotte after Fellner[illegible])

8 *Discoloration of the skin* The skin often becomes gray or brownish This is especially conspicuous in the white race The colored skin has a tendency to become lighter The skin sometimes takes on a senile and wrinkled appearance

9 *General symptoms* Chills fever anemia nausea weakness muscular pains, and other general symptoms of bacteremia and toxemia are very common The fever may be accompanied by profuse sweating during which the patient may notice that parts of his body remain dry

Lepromatous Leprosy.—In the lepromatous form the maculae show an early tendency to become infiltrated or nodular Nodules may appear in varying numbers and sizes often on apparently normal skin without any inflammatory halo The first stage may look like an acne papule then the lesion becomes firm shotty raised and glossy often with small telangiectasias The color is pink in the early stages later purple brown copper or bronze If regression occurs the epidermis of the lesions may peel. The lepromas are often warmer to the touch than the surrounding area Hyperesthesia and anesthesia are observed in almost all cases but the time of appearance and the site vary If cut the patient may feel the touch of the knife but no pain The lesions may coalesce and form plaques. Such large or small infiltrations may remain stationary for a long time and then resume their growth or undergo regression or ulceration which may partly by secondary infection reach a great depth and width especially in tropical countries The ulcers may finally heal with scars which reflect the degree of destruction All stages—infiltration single and coalescent nodules ulceration and scarring—may be encountered in the same patient at the same time so that an exceedingly multiform picture results The face is the main site of the nodular changes The forehead the eyebrow region the nose the chin the lobes of the ears and finally the entire face may become involved The development of the lepromas on the face is determined by the fibrous and muscular strictures. The fibrous strands crowd the infiltrates together into bulging tumors

[illegible] Frazier C N Leprosy Epidemiology and Natural History J A M A [illegible] 1943.
[illegible] Fellner M Leprosy—Review of Literature for 1940, Dermatologica [illegible] 121-125, 1941
[illegible] Fellner M Leprosy Dermatologica [illegible] 123-125 [illegible]

and divide them by deep creases. Thus the lion face the *facies leonina* of advanced tuberous leprosy results. Patients in this stage have an amazing similarity It may be difficult to tell from the face, whether the patient is young or old man or woman or even whether he is colored or white since the colored skin often becomes lighter and the white skin darker The nose becomes swollen partly by specific involvement of the nasal mucosa which may lead to complete destruction of the septum with subsequent collapse of the nose. It is surprising that the sense of smell resists destruction for a long time. Corresponding lesions appear in the mouth the pharynx and the larynx. There are infiltrations ulcerations and scars with resultant deformations and strictures The *eyes* become involved in nine out of ten fully developed cases. The scalp and Scarpa s triangle often remain free and the trunk generally is not as heavily involved as the face. The buttocks are common sites of large nodular plaques.



Fig [illegible] —Leproma ous leprosy (Courtesy Division of Dermatology Department of Medicine University of Chicago)

Involvement of the *lymphatics* causes elephantiastic changes, especially of the lower legs with all the complications of the syndrome such as recurrent erysipelas and fever ulcerations and finally mutilations. The external genitalia are commonly affected Every internal organ may take part in the process though with great variation In some cases the gastrointestinal symptoms dominate the picture in others respiratory or urinary complications dominate. The *course* usually stretches over many years even 2 or 3 decades although acute cases with exanthematic eruptions of lepromas on almost the entire skin

severe prostration of typhoid type and rapid fatal outcome are known The chronic course is more or less often interrupted by acute febrile episodes the lepra reactions or *acute attacks* which contrast strangely to the otherwise extremely chronic course If the reactions are long and relapsing they may precipitate the outbreak of lepromas and aggravate the course. On the other



Fig 131 – Leprosy Lepromatous eruption (Courtesy U S Marine Hospital, Carville La.)

hand however short reactions may exert a healing influence Urticaria perstans-like lesions of comparatively transitory character have often been seen to appear during the lepra reaction Existing lesions may become edematous erysipeloid or vesicular indicating a severe focal reaction Remitting fever arthritic pains and general swelling and tenderness of the lymph nodes may accompany the reaction The sedimentation rate is increased The lepromin reaction (see below) is negative



Fig 135 —Leprosy papular exanthem. (Courtesy U S Marine Hospital Carville La)



Fig 136 Leprosy Lepromas Courtesy Dr E R Kellersberger

J Jadassohn[88] was the first to interpret the lepra reaction as a phenomenon of allergy to the leprosy bacillus. This opinion is today widely accepted.[89] Between the attacks periods of relative well being and regression of the lepromas may set in making the patients hopeful and believing that they are on the road to recovery This hope is however too often deceptive Suddenly fever heralds



Fig 137 —Advanced lepromatous leprosy (Courtesy U S Marine Hospital Carville La)

a new outbreak, with the appearance of new or the enlargement of old nodules If the patient lives long enough the healing tendency becomes more pronounced and gradual transition into atrophy and scarring may reach an *arrested state* which amounts to heal ng Actual spontaneous and relatively sudden healing with regression of all lepromas occurs occasionally In such favorable cases the bacilli disappear from the nose and after long observation such a patient may be considered healed according to our present knowledge The neural form is more likely to become rrested than the lepromatous variety but arrest or healing is the exception in both types. Ordinarily the patient is condemned to a long period of increasing suffering The involvement of the air passages and the eyes the loss of voice the general induration and infiltration of the skin the nervous disturbances the pain the effort connected with the slightest movement the terrific odor diarrhea and many other afflictions among which the mental suf fering of being an outca t is not the least must make death appear as a salvation Pulmonary *tuberculosis* is a frequent complication and cause of death in ad vanced lepromatous leprosy

[89] Pardo-Castello V and Tiant F R Leprosy Correlation of Its Clinical Pathologic Immunologic and Bacteriologic Aspects, J A M A 121 1264-1268 1943

Neural Leprosy —Lepra nervosa generally takes on a still more chronic course than the tuberous form Cases of 60 years duration are on record and long periods of apparent arrest may occur

Fever and other general prodromes herald the cutaneous eruptions more frequently than in tuberous leprosy



Fig 128 Neural leprosy (Courtesy Dr [illegible] of Dermatology Department of Medicine University of Chicago)

In the early stages the appearance of all three types of maculae the red spots the pigmented spot and the white spots dominates the picture with a conspicuous absence of infiltrations and nodules. The distribution is usually fairly symmetric but varying in size and shape Symmetric erythema nodosum-like eruption occur The spots become anesthetic within a few days. Blisters are common and may predominate so that a pemphigus-like picture results. However Nikolsky's sign is negative The bullae may increase peripherally surrounded by an inflammatory vesicula areola. Large bullae may form destructive foul ulcers which heal slowly The ulcers are painless. In some cases no actual bullae develop but the epidermis forms a dry scaly crust of yellowish-brown color The predominantly bullous and ulcerative type of

leprosy is called *lazarine leprosy* The content of the blisters contains many bacilli but the tissues are able to destroy them quickly so that they cannot be found in sections. The lepromin reaction is positive indicating good defense The prognosis is relatively good [80]

Paresthesias hyperesthesia and anesthesia are the common complaints of beginning neuritis muscular atrophy paralysis and trophic ulcers follow later Some of the nervous complications which predominate in lepra nervosa have already been described



Fig. 130 —Lazarine leprosy (Courtesy U S Marine Hospital, Carville La)

The affected nerves often become thick spindle or rosary like so that they can be palpated Sometimes only a relatively small area of the skin becomes anesthetic, and the whole process may become arrested at this stage and stay so for a long time with no other symptoms until new similar crops continue the development

Anesthesia the most characteristic phenomenon of nervous leprosy leads to ulcers and to mutilation. The feet lower legs, hands and forearms are most commonly affected Beginning at the little finger the anesthesia may involve the whole arm in similar fashion a leg may become anesthetic. Later on symmetry is pronounced It must be stressed that anesthetic areas are not sharply bordered and that they do not exactly correspond to the nerve supply

The successive impairment of the senses of heat cold pain touch and pressure has been mentioned earlier Deep muscular and joint perception remains intact The mucosal surfaces may become anesthetic too. The scalp is seldom involved

Muscular atrophy usually starts in the small muscles of the hands, leading to a clawlike contracted hand which can hardly be moved Similar sequelae develop in the feet After an initial increase the reflexes disappear Neuralgic pains in the trigeminus area are common While total paralysis of the facial nerve is rare the muscles which close the eyes are frequently paralyzed Lagophthalmus ectropium loss of eyelashes nd dryness of the conjunctivae finally lead

to the characteristic rotunditas oculorum which since the middle ages has been known to be characteristic of the leper. The empty stare of such eyes, together with partial or total immobility of the face, creates the typical *facies antonina*.

The skin as already mentioned generally becomes wrinkled, ashen or pigmented. Gradually the sebaceous glands disappear. The nails may partially or totally atrophy and disappear.



Fig. 40. Leprosy. Mutilation. (Courtesy U. S. Marine Hospital, Carville, La.)

Mutilations follow anesthesia. The destructive process may start with an abscess or trophic ulcer. Resorption of bones, especially of the fingers, may be a factor. The middle phalanx may disappear first so that by contraction the first and third phalanges become drawn together. Ainhum-like strangulations are another feature. All the processes, anesthesia, muscular atrophy, trophic ulcers, bone resorptions, secondary infection and gangrene may finally lead to the complete loss of fingers, toes, hands, feet and even whole extremities.

It is not surprising that mutilation and all the other sequels of the nervous involvement finally lead to cachexia. It is however most amazing that life

frequently continues for long years in spite of such destruction and suffering in which the body is dead before the patient dies (Danielssen after Klingmüller)[??]

Lepra mixta combines features of both types. It is in some regions more common than the tuberous or nervous forms.

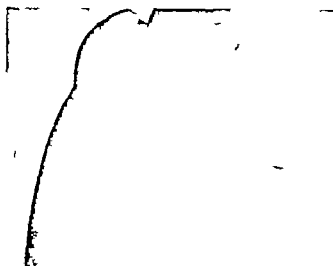


Fig. 141.—Leprosy M. Bathon. (Courtesy Dr E. R. Kellerberger)

Tuberculoid Leprosy (J Jadassohn[??]) —Besides the lesions of lepromatous and neural leprosy one may encounter round or gyrate flat smooth slightly discolored skin lesions which may be large or small The center is usually depressed and the edge slightly raised Often especially in the edge small lupoid soft nodules can be demonstrated which under the pressure of glass leave a yellowish spot. These show little resistance to piercing with a bulbous probe Anesthesia is not very marked but some authors found tuberculoid lesions very frequently in the neural type (Lowe et al after Wilcocks,[??] Ota and Sato after Klingmuller[??]) Some of these cases have sarcoidal features.[??] It seems to be quite certain that tuberculoid leprosy does not occur together with lepromas,[??] at least this combination must be very rare Tuberculoid leprosy is of greater theoretical than clinical importance because its tuberculoid structure and paucity of bacilli demonstrate the so-called law of J Jadassohn and Lewandowsky according to which tuberculoid structures are apt to appear where microorganisms or their products are destroyed by the local immune-biologic reactions (see page 180) In other words the immune-biologic defenses in tuberculoid leprosy are excellent which is in line with its relatively benign course (see also lepromin reaction)

These cases are generally rare though quite frequent in some small localities. They are more often seen in the Negro[??]

[??]Sulzberger [??] revised formulation with omission of the word rapidly since relatively slow destruction seems likely to produce tuberculoid structures

[??]Wilcocks C Summary of Recent Abstracts (Leprosy) Trop Dis Bull 40: 809-815, 1943.

[??]Bloegler W Allergic Reactions i Tuberculoid Leprosy Kli Wchnschr 19: [??]-[??] 1940.

Mucosal Manifestations —

The mucosae of the upper air passages are in almost all cases involved though in widely varying degree [364] The *nose* though rarely affected in neural leprosy has been found involved in the lepromatous variety in 33 to 96 per cent according to a great number of authors from many countries. The nasal mucosa is often the first site of lepromatous lesions and bacilli can often be found in the



Fig 112 Tuberculoid leprosy Courtesy U S Marine Hospital, Carville La)

nasal discharge when no other symptoms exist The vestibule which may be filled with crusts which have formed over ulcerating lepromas in the nasal mucosa proper is often the site of the same sequence of changes which takes place on the skin i.e. inflammation infiltration ulceration and scarring The infiltrates appear as tough yellowish-pink pinhead to cherry stone sized granulations which soften and ulcerate quicker than the corresponding skin lesions. The place to look for the lesions is the cartilaginous septum the vestibule and the lower turbinates Perforation of the nasal septum occurs in about 40 per cent of all types.

Oral infiltrations consisting of grouped small yellowish pink nodules are often found on the *palate* The pharyngeal reflex is lacking in 60 per cent

[364] Pinkerton, F J Leprosy of Upper Respiratory Tract T Amer Laryng Otol & Rhin. A MA pp. 97 118 1939

of the neural cases (Belowidon after Klingmüller[HI]) Scarring results in deviations of the uvula. The gums, the tonsils and the labial mucosa are less often involved The lips become more often affected in the skin and vermilion parts than in the mucosa proper



Fig 1[illegible] —Leprosy Leproma of the palat (Courtesy U S Marine Hospital, Carville, La)

On the *tongue* lepromatous lesions occur as flat yellowish or silvery glossy or tendinous discoid polygonal or streaky nodules or as diffuse infiltrations of the base of the tongue Generally the tongue resists the lepromatous involvement longer than other parts of the mouth The incidence of leprosy of the tongue given in various statistics from different countries varies from 5 to 50 per cent The same type of conglomerations of yellowish pink granulations as are found in the oral cavity occurs on the epiglottis and in the arytenoid area while the vocal cord usually resists for a long time The trachea is rarely affected and if so in the uppermost part.

The *lungs* may become lepromatous but this is relatively rare

The eye is very often affected In Norway in almost 100 per cent of the lepromatous and in 60 per cent of the neural cases The percentages of other countries are smaller but still considerable Lepromatous involvement of the lids madarosis specific conjunctivitis ectropion keratitis iritis episcleral lepromas lagophthalmus and its sequelae muscular disorders atrophia bulbi and many other lesion are well known[##]

The *auricle* especially the earlobe is a common site of lepromas while the ear duct usually stays free The internal ear is hardly ever affected

The *sebaceous* gland seem to be more active so that the skin over the leproma is oilier than normal On this phenomenon was based the medieval "water test. If the skin did not become wet from water the patient was assumed to be a leper

Perspiration may within the affected areas be increased in the early stages and then paralyzed The loss of perspiration may be due to specific destruction of the sweat glands or to nervous disturbance.

The *hair* of the body and the beard may early become dry brittle and thin The early loss of the lateral third of the eyebrows has often been emphasized The hair of the head is as a rule surprisingly resistant even in advanced cases, but is lost in the affected areas.

Heller [384] in his monograph on the diseases of the *nails* reports thinning longitudinal grooves and shedding Occasionally the nails withstand the advance of the disease surprisingly well so that normal nails can be seen on severely affected fingers of mutilated hands. Complete and permanent loss, or reduction of the nails to tiny horny cones are characteristic of the terminal stages.

Pathological Histology—There are three types of pathological changes caused by the leprosy bacillus the infective granuloma the nonspecific inflammation and the tuberculoid structures (Lewandowsky after Klingmüller) [385] Furthermore the Hansen bacillus may be found in tissues without causing any changes. The *lepromatous* changes start most often in the walls of the vascular plexus surrounding the follicles, the arrectores pilorum the sweat glands the central vessels of the papillae and the cutaneous nerves. These early localizations are indicative of a hematogenous infection. The infective granuloma consists of lymphocytes, plasma cells epithelioid cells and giant cells. Usually the lepromas contain great numbers of bacilli arranged in bundles or loose groups between the cells In the capillaries of the papillae in the lymphatics and in round dense intracellular conglomerations in the cells which are known as globi Globi often contain more bacillary granula than rods and may become large enough to be macroscopically visible The intracellular bacilli are mostly found in the lepra cells which are large polynuclear cells with a foamy protoplasm. The lepra cells stem from histiocytes and as such they are part of the reticulo-endothelial system Their protoplasm is rich in lipids. Before the leproma invades the epidermis, it stays for a certain period separated from it by a characteristic leprosy free layer of tissue a phenomenon which A Neisser had observed

Neural leprosy is characterized by interstitial neuritis. Absence of granuloma formation is striking The histology of *tuberculoid leprosy* resembles that of Boeck sarcoid The lesions consist of sharply bordered perivascular granulomas sometimes with a necrotic caseating center Plasma cells are scarce, epithelioid cells abundant Giant cells of the Langhans type complete the tuberculoid picture Frazer[386] says that the most typical tubercles of the skin are found not in tuberculosis but in leprosy

The invasion of the nerves may be metastatic and hematogenous or contiguous from the skin The latter is very common and explains the predominance of very peripheral neural changes in sensory nerves over motor paralyses.

Tests and Diagnosis.—Allergic and serologic reactions have not become as important in the diagnosis of leprosy as in other diseases. In advanced cases the Wassermann and Kahn reactions are often positive. While many

believe that these are nonspecific reactions some more recent investigators (Gundersen Ole Berner after Fellner[963, 964]) believe that a positive Wassermann in a leper means syphilis

Rubino's[965] *reaction* based on the sedimentation and agglutination of prepared mutton erythrocytes with the test serum is negative in nonlepers[966-968] often positive in lepers especially in the tuberous form

Some lepers react to *tuberculin* probably without being tuberculous. The serum of nontuberculous lepers may give a positive complement fixation test for tuberculosis. These occasional difficulties are further increased by the frequent tuberculous infection of advanced lepers[146, 968] (Babes after J Jadassohn[969])

The serum of lepers is highly toxic to growing young *plants*[970] in contrast to the serum of patients with syphilis or tuberculosis.

Allergic skin reactions with allergens derived from *lepromas* have become important.[971, 972] Silent immunization in leprous surroundings and anergy must be considered in the interpretation

The *Mitsuda*[971] reaction is not so much used to establish the diagnosis of leprosy as to test the immune-biologic defense of a patient in order to gain a basis for prognosis The test consists of the intracutaneous injection of 0 1 c.c. of lepromin an extract from lepromas[971] If the reaction is positive a papule develops in the second week. It reaches its acme in the fourth week with a nodule ½ — 1 cm in diameter which eventually may ulcerate and slowly heal The papule has a tuberculoid structure The test is often positive in healthy persons from leprous surroundings and in tuberculoid leprosy it is often negative in lepromatous leprosy and doubtful in cases with histologically non specific inflammatory lesions. The negative lepromin reaction in lepromatous lepra with abundant bacilli is explained by a lack of defense to the infection and is therefore considered a bad prognostic sign. The positive reaction is considered as an indication of vigorous defense and relatively favorable prognosis (see tuberculoid leprosy and law of Jadassohn and Lewandowski pp 180 and 242)

Febrile and focal reactions to 0 2 to 3 0 grams of *potassium iodide* or to intravenous injections of sodium iodide occur frequently in lepers and have diagnostic value The serologic reactions may become activated and the increased nasal secretion may lead to the detection of leprosy bacilli in smears

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[965] Rubino M C Séro-diagnostic de la lèpre par l'agglutino-sédimentation des globules rouges de mouton formolés, Bull Acad de méd Paris 106 800-803 1931 also Ann Inst Pasteur 47 147 172, 1931

[966] Lépine P Markianos, and Papayoannou, A Valeur pratique de la réaction de Rubino pour le sérodiagnostic de la lèpre, Bull Soc path exot 25 843 1932 Zbl 43 402.

[967] Hombria M Zum serologischen Studium der Lepra, Actas dermo-sif 25 193-200 1933 Zbl 44 635

[968] Montañes, P Diagnostischer Wert der Rubino-schen Reaktion bei Lepra, Actas dermo-sif 24 241 263 1932 Zbl 41 840

[969] Brants, J Erythrocytensenkungsreaktion bei Lepra Lat arst Zurn 11 619-633 1932 Zbl. 44 33 1933

[970] Macht, D J Phytopharmacologic Studies on the Sera of Pemphigus, Syphilis, and Leprosy Acta dermat Kyoto 18 126-137 1933

[971] Mitsuda, K Troisième conférence internationale de la lèpre Communications et débats Paris 1924 J B Baillière et fils

[972] Bargehr P [illegible] Hautreaktionen bei Lepra, Ztschr f Immunitätsforsch exper Therap 47 529-531 1926

which were previously negative *Biopsy* of the skin or nasal mucosa testing of the serum of blisters produced by carbon-dioxide snow and puncture of lymphatic nodes are some of the laboratory methods successfully used to find bacilli For the preparation of *nasal smears* the mucosa should be gently scraped without causing bleeding

Clinical similarity to a great number of dermatoses may develop in one or the other stages of this chronic disease Psoriasis ichthyosis mycosis fungoides leukemia blastomycosis syphilis lupus erythematosus, vitiligo and a number of other skin diseases may occasionally be suggested by atypical leprosy

The course the occurrence of leprosy in the surrounding region macules and lepromas biopsy and above all anesthesia will usually decide the question If the cooperation of the patient in testing of the sensory functions is lacking the *histamine test* may prove valuable The skin is pricked with a needle through a drop of histamine salt solution 1 — 1000 In paralysis of the sensitive nerve endings a wheal appears as in the normal skin but it lacks the red areola which is normally seen This is called a negative histamine test Pardo-Castello and Tiant[illegible] found this test negative in the cutaneous lesions of leprosy The most difficult problems however may arise from nervous diseases and particularly from syringomyelia Here the anesthesia is more sharply bordered and the muscular atrophy (which in leprosy is usually restricted to the anesthetic parts of the hands) affects the arms and shoulders. Scoliosis bulbar symptoms pathological fractures of the long bones ataxia central unilateral facial paralysis tremor spasms—in short central neurologic symptoms and signs—are more suggestive of syringomyelia. The neural phenomena of leprosy are usually of peripheral character

Treatment —No specific therapy is known The derivatives of the chaulmoogra oils which are obtained from several tropical trees are so far the most effective drugs Recently promin a sulfone derivative has given encouraging results.[illegible]

[illegible] Faget G H Pogge R Johansen F A Dinan J F Prejean B M and Eccles, C. G Promin Treatment of Leprosy Pub Health Rep 58 1729-1741 1943

CHAPTER XIII

DERMADROMES OF INTOXICATIONS

A poison may cause a dermatosis by external contact without systemic interference (discolorations by dyes necroses by caustics) or by damaging the skin as part of the damage to the entire system In the latter case one must separate the intoxications in the strict sense from the allergic reactions. In *intoxications* the causative agent is toxic to all individuals if it is absorbed in a certain dose the damage it produces depends on the nature the amount and concentration of the poison and also on the length of time it acts excessive doses being lethal. The poison can be excreted and antidotes may reverse the process. There is no incubation period and the agent may be found in the tissues by chemical analysis These are some of the features characterizing intoxication in contrast to allergy (Tzanck after R L Mayer[974])

Thallium alopecia and argyria are examples of this, sometimes called cla sical type of toxidermia.

In the case of *allergic reactions* a specific alteration in the capacity to react acquired by previous exposure to the agent [974] is the dominant pathogenetic factor though the nature and dose of the poison (allergen) should not be under rated The allergic dermatoses have been the subject of several recent monographs[975 976] and their character as a manifestation of internal disorders is not yet clearly enough understood to warrant more than a short mention in this book. The dermatoses caused by metabolic and bacterial toxins are being dealt with in other chapters Thus only the *skin manifestations of systemic poisonings* in the strict sense of the term shall be discussed in the following chapter

Arsenicals

Arsenical poisoning occurs in a great variety of circumstances. It is an industrial hazard in the mining and smelting of many ores especially gold and copper The gases from the copper furnaces, the commercial metal sulfides as well as sulfuric acid are often contaminated with arsenic. Lead arsenite calcium arsenite and Paris green are rat poisons and agricultural insecticides used on such important crops as cotton tobacco apples grapes and vegetables.[977] Several arsenites sulfides of arsenic and other compounds are bright colored pig ments which in spite of modern paints and legislation have been and probably still are in occasional use in wall paints wall papers toys and colored papers

Medical administration of arsenicals is a common cause of arsenicism Suicidal and homicidal attempts and laboratory and industrial accidents are

[974] Mayer R L Toxicodermien Handb d H Gk 4 2 1 252, 1933

[975] Sulzberger M B Dermatologic Allergy Springfield, Ill 1940 Charles C Thomas

[976] Urbach E Allergy New York, 1944 Grune & Stratton

[977] Ayres S J and Anderson, N P Cutaneous Manifestations of Arsenic Poisoning Arch Dermat & Syph 30 33-43 1934

relatively rare by comparison. Mass poisonings affecting many thousands of people and remaining unexplained for a long time have occurred in a great number of instances. Such a so-called epidemic terrified Paris in the 1830's. About 40 000 persons became victims of a disease then called acrodynia which later was identified as arsenic poisoning. In later epidemics the cause was established by means of modern chemistry. There were several mass poisonings by wine from vineyards where arsenicals had been used for spraying. The last one occurred on ocean liners in 1932.[977-978]

In 1900 sulfuric acid containing arsenic, used in converting cane sugar into invert sugar for beer brewing in England, caused one of the greatest mass poisonings in history. Drinking water contains arsenic in toxic amounts (more than 0.2 mg. per 1000 c.c.) in many localities (Kathe after R. L. Mayer[974]). Chronic skin manifestations are likely to be found among the inhabitants as was shown in the description of the drinking water epidemic in the little Silesian mining town of Reichenstein.

The descriptions of these epidemics (partly given by such masters of dermatology as Vidal, Barthélemy and A. Neisser and their schools) laid the foundations of our present knowledge of arsenical intoxication which is one of the best studied of all human poisonings.

Acute arsenical poisoning is characterized by severe gastrointestinal symptoms which resemble cholera and may cause death in a short time, often after a few hours. Excessive lacrimation and salivation are early manifestations.

Within a few days or a week polyneuritis with multiple paralyses may develop together with cutaneous symptoms and may last a long time. Formication, pruritus, numbness, wrist drop and tabes-like syndromes are characteristic neurologic symptoms. There exist a great variety of clinical pictures, e.g. psychoses and agranulocytosis, but nervous and cutaneous symptoms are significant if not the dominating features of the subacute and chronic cases.

The *diagnosis* of arsenic poisoning[977] depends on the history, clinical appearance, and the presence of arsenic in the urine or hair in an amount which is decidedly above, or a multiple of, the value which may occur under normal conditions. Geographic location, drinking water peculiarities of the soil or a diet rich in seafood which may contain as much as 8 mg. per kilogram are factors which must be considered. Representative normal figures have been stated as 9.7 mg. per hundred grams substance for the hair and skin, 17.2 mg. for the nails and 10.4 mg. for the urine.[979] Wilcox[980] and Ayres and Anderson[977] recommend the Gutzeit test for urinary analysis which is a relatively simple color test.[981]

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[977] Thorel and Vieren. A propos d'une intoxication collective par l'arsenic, Ann. de dermat. et syph. 3: 614-621, 1932.

[978] Mühlens, P. Ueber eine Massenvergiftung nach Weingenuss an Bord, Deutsch. med. Wchnschr. 1932 I: 644-653.

[979] Billeter, O., and Marfurt, E. De la teneur normale en arsenic dans le corps humain, Helvet. chim. acta 6: 780-784, 1923.

[980] Wilcox, W. Acute Arsenical Poisoning, T. Med. Leg. Soc. Lond. 23: 6-162, 1930.

[981] Autenrieth, W. Detection of Poisons, ed. 4, Philadelphia, 1915, P. Blakiston Son & C

Sometimes it is possible to demonstrate arsenic in the biopsy specimen of skin lesions.[943-944] A progressive diminution of arsenic in the urine with clinical improvement under sodium thiosulfate therapy and the recurrence of symptoms on exposure to arsenic would be further proof. A positive patch test would show that there has been enough exposure to arsenic to produce sensitization.

Dermadromes.—The earliest skin manifestation of arsenical poisoning is *pruritus* which in some cases is restricted to the palms and soles. Conjunctivitis coryza and *puffiness of the eyelids* are also early warning signals which are observed more often in the course of prolonged arsenical treatment than after acute poisonings with one large dose. Other frequent and early symptoms are dis-



Fig. 144.—Exfoliative dermatitis (erythroderma) following arsenic poisoning. (Courtesy Dr. Garrett Cooper.)

tinctly bordered *palmar and plantar erythemas*. Their diagnostic importance is great because of the ease with which they can be noticed in ambulatory patients under continual arsenic treatment. The accumulation in the sweat glands which concentrate and eliminate the arsenic (Hutchinson after Ullman[945]) as well as the arsenophile keratotic epidermis are responsible *for the site of the erythemas*. *Palmar plantar sweating* is known as an early symptom.[946]

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[943] Osborne, E. D.: Microchemical Studies of Arsenic in Arsenic Dermatitis, Arch. Dermat. & Syph. 18: 37, 1928.
[944] Osborne, E. D.: Microchemical Studies of Arsenic in Arsenical Pigmentations and Keratoses, Arch. Dermat. & Syph. 12: 773-780, 1925.
[945] Ullmann, K.: Ueber Arsenexanthema ... im Bilde akuter wie chronischer Arsenvergiftungen, Klin. Wchnschr. 1931 II: 1505-1508, 1544-1549, 1931.
[946] Nissens, R. D. G. P.: Skin Manifestations in Arsenic Poisoning, Nederl. tijdschr. v. geneesk. pp. 5367-5369, 1935; Zbl. 53: 193.

Widespread or even truly generalized *rashes* following the intake of arsenicals may be seen together with or following the palmar-plantar erythemas.

Scarlatiniform morbilliform and *erysipeloid* erythemas are also known. Of greatest importance are the *eczematoid eruptions* which if further intake of arsenicals is not halted may rapidly develop into generalized exfoliative dermatitis which is such a great hazard in the use of the arsphenamines (see there) while it is rarely provoked by the inorganic arsenicals.

Generalized rashes may also be urticarial vesicular or bullous. K. Ullmann[187] emphasizes the sequence of pruritus urticaria and edema followed by circumscribed and later generalized erythemas.

The generalized exanthems may also appear as large or small scaly patches in some instances *resembling pityriasis rosea* or *parapsoriasis* Older lesions of this kind may have a heavier covering with scales and thus imitate *psoriasis* closely The arsenical erythema may also surround and accentuate pre-existing psoriatic lesions.[87]

The eruptions sometimes *imitate lichen planus* This is a remarkable fact with regard to the great efficacy of arsenic in lichen planus. No generally accepted explanation for this clinical coincidence has been offered and cannot be expected before more about the etiology of lichen planus is known

Scleroderma, as a probable arsenical sequel [174, 188, 189] has been observed in a considerable number of instances. Generalized *poikiloderma* as a permanent damage after arsenical dermatitis, is also on the long list of rare arsenical arsphenamine reactions [190] Recently nine cases of *acrodermatitis chronica* atrophicans have been observed in a group of wine growers affected with occupational arsenicism [191]

Edema is a common symptom in arsenical eruptions. There may be onl light puffiness of the eyelids and cheeks, but generalized edema is hardly ever absent in the severe forms of dermatitis.

Petechiae and other *hemorrhagic* symptoms are of rather grave prognostic significance.[18] *Herpes zoster* is reported to occur in 1 8 [192] 8[193] or even 10 to 20 per cent[192] of the cases. The high incidence of herpes zoster in the English beer epidemic was one of the facts which pointed to arsenic as the causative factor

Pustules, ulcers, necroses and perforations of the *nasal septum* are caused by the local external caustic effect of the arsenic.

The *oral mucosa* may participate early in the toxic syndrome with pharyngitis and gingivitis. Ulcerative stomatitis or glossitis may occur in severe cases.

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[187] Ullmann K. Arsenkeratose und Arsenwarzenbildung, Zbl. 36 314, 1931.

[188] Ayres S. J. Scleroderma. Possible Manifestation of Chronic Arsenic Poisoning, Arch. Dermat. & Syph. 2: 747 1920

[189] Ayres S. Jr. A Fifth Case of Scleroderma With Arsenic in the Urine Arch. Dermat. & Syph. 3 245-247 1921

[190] Cannon A. D. Karelitz Karry M. D. and Fischer J. K. Poikiloderma-like Changes in Skin, Following Arsphenamine Dermatitis, J. A. M. A. 118: 123-128 1942

[191] Braunschweig H. Acrodermatitis chronica atrophicans bei Winzern mit Arsenschädigungen, Arch. f. Dermat. u. Syph. 179 697 702 1939

[192] Nielsen Herpes zoster während As-Behandlung, Monatsh. f. prakt. Dermat. 31: 302, 1900.

[193] Geyer L. Chron. Hautveränderungen beim Arsenicismus und Betrachtungen über die Massenerkrankungen in Reichenstein in Schlesien Arch. f. Dermat. u. Syph. 43 221, 1898.

The *hair* is almost always diffusely shed The alopecia is complete in severe cases of arsenical dermatitis.

The *nails* usually record severe dermatitis as well as acute especially single-dose poisonings by cross furrows (Beau s lines) or with white[894] or gray cross lines. The latter have become known as Mees bands[894, 895] and are often associated with polyneuritis arsenicosa. They are dull glistening bands extending across the breadth of each finger nail The bands appear at the lunula about *eight weeks after the poisoning If one adds 10 days for every 1 1 — 1.2 mm* of the distance from the proximal border of the lunula to the distal border of a band one can determine the approximate date of the poisoning The arsenic content of a band has been found to be 10 times higher than in the undiscolored parts of the nails.[896]

The condition is apparently identical or similar to the leukonychia striata which was observed in many instances during the English beer epidemic and in other instances of arsenical poisoning The nails may be shed after severe arsenical dermatitis

Arsenical dermatitis of all types heals with *hyperpigmentation* of varying intensity which may even develop without preceding noticeable inflammation

The distribution depth and duration of the hyperpigmentation vary within wide limits. The areas which have a natural tendency to darken such as the genitals, groins umbilicus and mammillae as well as scars healing skin lesions and pressure and friction points are often highly pigmented [896]

The indi idual tendency to pigment has a much greater influence on the melanosis than the size of the doses of arsenic. *Melanosis may appear as early as 12 days after the onset of arsenical medication and after small doses.* On the other hand severe poisoning may fail to produce it. This is well demonstrated by the fact that in poisoning from drinking water with generally equal supply to the population only some persons develop marked melanosis. The discolora tion may start insidiously and reach any even the severest degree [897]

The diffuse type of arsenical melanosis is so similar to the appearance of Addison s disease that during the great beer epidemic in England most cases were so diagnosed until the autopsies failed to reveal adrenal changes. The covered parts of the skin seem to darken more than the open ones [874] although *the face is frequently affected In a minority of the cases a dense regularly* reticulated or dappled pattern of pigmentation and depigmentation may cover wide areas especially the back. This type of arsenical melanosis has been called *raindrop pigmentation* because of its resemblance to a window pane covered with raindrops. This characteristic type of arsenical pigmentation is often found in chronic arsenicism due to drinking water or prolonged administration of *inorganic arsenicals*

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[894] Mees, R A Een verschijnsel bij polyneuritis arsenicosa, Nederl Tijdschr Geneesk 1919 I 391-396

[895] Barker L F Exfoliative Dermatitis in Accidental As-Poisoning Mees Band Urol & Cutan. Rev 46 635-637 1942

[896] Wigand R Das Meessche Nagelband bei Polyneuritis arsenicosa, München med Wchnschr 87 633-634 1940

[897] Throne B Arsenical Pigmentation Arch Dermat & Syph 21 479, 1931



Fig. 145. Arsenical melanosis "raindrop" appearance. (Courtesy Division of Dermatology, Department of Medicine, University of Chicago.)



Fig. 146.—Arsenical melanosis "raindrop" appearance.

Arsenical melanosis has also been seen to follow the pattern of underlying large veins [774]

The *depigmenting* tendency after arsenical dermatitis is best observed in Negroes [893]

In rare instances the *oral mucosa* participates in the pigmentation although the lack of oral pigmentation has often been emphasized as a differential criterion against Addison's disease The arsenical melanosis may vanish rapidly with the other symptoms of the intoxication but more often it persists much longer or even permanently

The arsenical pigment is *melanin*[894] and as such is iron free It can be distinguished from arsenic crystals[894] which lie mostly between the cells.



Fig 147 —Arsenical keratoses of palms after indiscriminate use of Fowler solution in psoriasis

Keratoses are the most common and characteristic and the most easily detectable of all skin manifestations of chronic arsenic poisoning

The keratoses may appear within a few weeks after the start of arsenic intake or as late as many years after the medication or other exposure has been stopped [895] An erythema may or may not precede their appearance

The characteristic sites of the hyperkeratoses are the palms and soles with their peculiar affinity for arsenic The areas of friction and pressure which normally tend to callus formation are especially apt to develop arsenical hyper

[893]Cannon A B and Karelitz, M D Vitiligo From Arsphenamine Dermatitis and From Arsenic Arch Derm & Syph 28 642-6 1 1933
[894]Gans O Histologie der Arsenmelanose Beitr path Anat allg Path 60: 222-34, 1915
[895]Montgomery H Arsenic as an Etiologic Agent in Certain Types of Epithelioma, Arch. Derm & Syph 32: 218-236 1935

keratoses. Thus the plantar arch and the center of the palms remain relatively free from circumscript lesions but they are not immune against diffuse keratosis. Occasionally circumscribed keratoses may appear on the back on the chest on the extensor surfaces of the elbows and knees, on the heels, or on the dorsa of the hands and feet [illegible]

Hyperkeratoses may be diffuse and cover the entire palms and soles. Much more characteristic, however are the circumscribed lesions. They are often called warts but they are less circumscribed and vascular than ordinary warts They are cornlike accumulations of horny tissue and because of their completely epidermal structure they are more transparent than warts or corns. Their color is usually pale yellow but thicker layers may take on a dirty gray or even slate or brown hue. The opening of a sweat gland is sometimes visible at the top of a small lesion The size varies from that of a millet seed to a pea or even an almond *Hyperidrosis* is a frequent annoying accompaniment which may even be the presenting symptom in cases of arsenical keratosis.



Fig 4 Transition of arsenical keratosis in cancer

There exist only a very rough parallel between the appearance of the keratoses and the dose and length of time of arsenical exposure. Examples of extensive keratoses after small amount of arsenic and complete lack of keratoses after huge doses are well known [illegible]

Chronic intoxication with inorganic arsenical is especially apt to cause keratoses while they are rarely seen among the tremendous numbers of people treated with arsphenamines The circumscribed keratoses usually disappear

[illegible] Kumer L. Mächtige papillomatöse Wucherungen auf chronischer Haut, Zbl. [illegible] 640, 1936

PLATE II

1 Lupus erythematosus acutus. Rapidly fatal case.

2 Arsenical keratosis with carcinoma

3 Leaking aneurysm of the abdominal aorta. Giant ecchymoses.

4 Hypertension. Chronic nephritis. Pruriginous eruption

5 "Vagabond" skin

6 Erythema palmare. Mitral insufficiency













PLATE II

gradually with the elimination of the arsenic. Sometimes however they are permanent. If they are removed they grow back rapidly. Such keratoses of many years standing are *precancerous* lesions.

Montgomery[1000] saw *epitheliomas* develop in 20 per cent of his 85 cases of arsenical keratosis but the percentage is likely to be smaller in less preselected material than is encountered at the Mayo Clinic.

The cancers are usually of the squamous cell type. Some assume features of Bowen's disease by the formation of grouped or circinate lenticular crusty or scaly papules. But it has not been sufficiently proved that Bowen's disease and superficial epitheliomatosis generally are due to arsenic as had been suggested.[1001] Arsenical epitheliomas may also appear independently of keratoses. They may occasionally look like superficial epitheliomatosis forming thin scaly plaques which however often lack the thin threadlike pearly border of this variety of skin cancer.[1001]



Fig. 49 — Arsenical keratosis resembling Bowen's disease.

Basal cell epithelioma is very rare. The degree of malignancy is relatively low metastases occurring very late. Arsenical cancers of the urethra bladder and bronchi have been observed in rare instances.[1002]

The cancers are not very malignant. They metastasize late and are seldom and only after a long time destructive. They respond well to radiation and even the excision of relatively large cancers may be successful. In all cases of

[1001] Anderson, N. P. Bowen's Precancerous Dermatosis, Benign Superficial Epithelioma, Arch. Dermat. & Syph. 26: 1052, 1932.

[1002] Goeckerman, W. H. and Wilhelm, L. F. X. Arsenic as Cause of Cancer of Mucous Membranes, Arch. Dermat. & Syph. 42: 641-64. 1940.



Fig. 160.—Large arsenical cancer over Achilles tendon. Indiscriminate use of Fowler's solution against psoriasis.

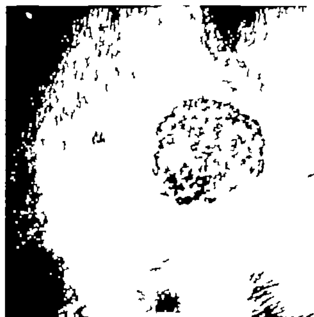


Fig. 161. Superficial epitheliomatosis in a patient with arsenical keratoses and history of indiscriminate use of Fowler's solution.

multiple epitheliomas of the skin the possibility of an arsenical etiology should be considered [illegible]

Arsenical keratoses should be *treated* by any superficially destructive measure such as dry ice fulguration etc. The use of keratolytic salves gives only temporary results. The value of sodium thiosulfate medication either by the intravenous injection of 1 gram daily or by mouth is controversial

Arsenical epitheliomas should be treated like other skin cancers.

Arsphenamines.—The dermatoses due to the use of arsphenamines are either arsenical in character or they are specific allergic phenomena.[illegible]

The *angioneurotic syndrome* or nitritoid reaction occurs immediately after an intravenous injection of any one of the arsphenamines particularly if the injection has been given at a fast rate

Itching may be the first symptom of this reaction but it is quickly followed by a feeling of great congestion and pressure in the head dyspnea palpitation and anxiety There is acute redness of the face as if the patient had inhaled amyl nitrite The face may become acutely swollen Soon the bright erythema becomes cyanotic and in severe cases the patient may become unconscious and the breathing stertorous. The terrifying episode is usually over after a few minutes, especially if adrenalin is injected Death has rarely occurred [1] An exceedingly slow rate of injection change of the type of arsphenamine and lowering of the dose are the best means of *prevention*

Urticarial or in rare instances bullous rashes appearing in the same site immediately or shortly after the injection are called *fixed* arsphenamine eruptions

The severest cutaneous disease following the administration of any one member of the arsphenamine group is *generalized exfoliative dermatitis* This dangerous dermadrome usually starts after several injections have been given or not infrequently a few weeks after the series of injections has been finished

Fever anorexia and slight erythema often precede the main rash which appears first on the extensor aspects of the knees and elbows as a morbilliform or scarlatiniform eruption. Within a week it develops into generalized acute erythroderma There is usually widespread or even generalized weeping edema fever albuminuria and hepatitis. Septic symptoms especially multiple boils and foci of cellulitis and necrosis are a prominent feature. This may last for many weeks. Gradually the skin dries up and is exfoliated in large sheets especially about the hands and feet. Melanosis of moderate degree follows frequently There is always diffuse effluvium of the hair and often the entire hair falls out. The nails may also be shed The prognosis is most dubious. Death from sepsis occurs frequently

A large recent American series gives the incidence of severe crustaceous dermatitis as 0 7 per 1000 injections. The patients were not previously treated with arsphenamine [illegible] This seems much higher than other observations

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[illegible] Birnbaum, G Salvarsanschädigungen der Haut, [illegible] 49 97 106 1936

[illegible] Welsh, J R and [illegible], E. Severe Reactions to Arsphenamine Among 2040 Patients Previously Untreated Ven Dis Inform 21 [illegible] 1940.

Allergy to arsphenamines in cases of dermatitis has often been demonstrated by positive patch tests.[1995] Women were twice as often affected as men [1995]

The *treatment* requires daily injections of 1 gram of sodium thiosulfate and best nursing care. Penicillin is probably helpful in combating pyogenic infection Liver extract has often been recommended

Convalescents should not be subjected to any further arsenical treatment.

Early acute arsenical erythema or *erythema of the ninth day* is a febrile multiform rash of unknown etiology occurring in about 3 per cent of the patients treated for the first time with trivalent arsenicals [1996] The rash is described as generalized and composed of irregularly macular or morbilliform lesions clearing up after 2 days Arsenical treatment may be continued with extreme caution only but is better replaced by penicillin [1997]

Other rare eruptions following the use of arsphenamines include *lichen planus* and *lichen spinulosus* [1998] *Jaundice* is a frequent after-effect of arsphenamine treatment. There is no consensus whether arsphenamine alone allergy syphilis, another infection or a combination of factors are responsible for the frequent cases of hepatic disease in the course of antisyphilitic treatment with neoarsphenamine [1999]

Gold

Gold poisoning is almost exclusively due to medication gold-sodium thiosulfate (sanocrysin) being the most widely used compound The general symptoms follow the pattern of other heavy metal intoxications including arsenic. There may be nephritis, enteritis hepatitis and a depression of the hematopoietic system in severe cases ending in agranulocytosis or aplastic anemia.

Ill effects mostly of a mild nature were estimated to occur in about 10 per cent of 1400 tuberculous patients treated with gold compounds.[2000] They were much more common in the early days of gold therapy when high doses were advocated

Dermadromes —The skin is most often affected [2001] The injection of a gold salt even in small quantity may cause immediate or early *nitritoid reactions* with a flushed face and a sensation of giddiness sometimes with severe cervical pain Such reactions occurred most frequently after sodium thiomalate (myochrysin) [2001,2002] They are very rare after gold sodium thiosulfate if it is injected slowly into the vein

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[1995] Schoch, A G The Patch Test and the Element of Syringe Contamination in Arsphenamine Sensitization Dermatitis, J A M A 99 1267 1932

[1996] Cañizares, O and Thomas E W Early Acute Arsenical Erythemas, Arch Derma Syph 39 467 1939

[1997] Leifer W Danger of Continued Arsenotherapy in Cases of Erythema of Ninth Day Am J M Sc. 210: 455, 1945

[1998] Volavsek, W Seltene Salvarsanschäden Derma Wchnschr 116 409-420 1943

[1999] Winkler M Dermatitis and Icterus Following Arsphenamine and Bismuth Therapy of Syphilis Dermatologica 81 297-309 1940

[2000] Mayer O Gold Treatment of Pulmonary Tuberculosis Brit J T berc 28 121 139 1934

[2001] Fellner M Die Goldtherapie in der Dermato-Venereologie ibid 43 33 1932

[2002] Lintz, R M Toxic Reactions With Gold Salts in Treatment of Rheumatoid Arthritis, J Lab. & Clin Med 26 1629-1634 941

[2003] Nicolas, J Lebeuf F and Mollard H Sur quelques accidents inédits de la chrysothérapie (une crise nitritoide) et de nouvelles localisations tuberculeuses, Bull Soc franç d dermat et syph. 39 574-578, 1932

All the familiar types of toxic exanthems have been observed. Morbilliform and scarlatiniform rashes are relatively common multiform and bullous eruptions are rare.

Some exanthems resemble pityriasis rosea but they lack the primary lesion. [illegible] Itching may be the first symptom of all these rashes and should be reason to discontinue the treatment.



Fig. 132 Acute severe, extreme old eruption provoked by gold therapy of chronic lupus erythematosus

Hemorrhagic eruptions seem to occur more frequently than in arsenical poisoning [illegible] The tuberculosis or syphilis of the patients treated with gold may hav some importance in the pathogenesis of the purpuric [illegible] mostly petechial rashes These eruptions are frequently accompanied by other hemor rhagic phenomena especially hematuria. Naturally all hemorrhagic mani festations are potentially serious *Generalized exfoliative dermatitis* with loss of hair and nails though rarely with a fatal outcome [illegible] has been observed [illegible]

Lichen planus-like eruptions seem to be a feature of the gold dermatoses.[illegible] They may be subacute with violent itching vesicles and blisters or even turn into generalized exfoliati e dermatitis. More commonly they consist of relatively

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[illegible] Wile U J and Courville C J Pityriasis-Rosea-Like Dermatitis Following Therapy With Myochrysine Arch Derm & Syph 42: 105-1112 1940.

[illegible] Emile-Weil P and Demmer J Les états hémorragiques post-auriques Sang 6 [illegible] 1932

[illegible] Gougerot, H and Blum, P Syndrome hémorrhagique déclanché tardivement par l or Bull Soc franç de dermat et syph 40 677-678 1933.

[illegible] Martenstein, H Die Behandlung des Lupus ery hema odes mi Krysolgan, Klin Wchnschr 1 [illegible] 1933

[illegible] Bellafante A J G Onychia and Alopecia After Gold Dermatitis Nederl tijdschr Geneesk. pp 3012-3014 1937 Abst [illegible]

[illegible] Milian, G L Lichen Planus Due to Gold Therapy Bull Soc franç de dermat et syph 46 39-42 1939

large flat papules which have a tendency to coalesce into large plaques of the lichen corneus type.[1031]

There are two kinds of skin *discoloration* known to follow the administration of gold. One is caused by deposits of *melanin* in the upper cutis. This type corresponds to the more common arsenical melanosis and is reversible. It frequently develops after gold rashes [1032] but it may also be primary and occur after small doses [1033]

The second type is of greater and more practical interest. The injected salt is reduced to *metallic gold* and deposited in the lower cutis in the subcutis in the kidneys and in all parts of the reticulo-endothelial system

The visible discoloration is restricted to the skin exposed to light. No difference in the gold content between discolored and apparently normal skin can be found by means of spectroscopic or histologic analysis.[1034] With the slit lamp gold particles can be demonstrated in the cornea.

The darkening is diffuse and slate to graphite gray in color Most observers emphasize a bluish or purplish hue [1035] The dyschromia seems to be permanent. Lorenzen[1036] found that none of his tuberculous patients who had received more than a total of 0 15 Gm. of sodium aurothiosulfate per kg body weight escaped chrysiasis but none of those with a total of less than 0 05 Gm per kg developed it. The trouble becomes visible one to three years after the treatment. Mild cases of *chrysiasis* as this discoloration caused by gold deposits is called do not as a rule constitute a very conspicuous disfigurement.

With the commonly used doses of up to 50 mg per injection the danger of producing chrysiasis is remote

Hyperkeratoses and diffuse keratoderma after gold treatment are very rare. [833,1037]

Oral symptoms of gold eruptions have frequently been described. Dryness and metallic taste are often the first symptoms of gold intolerance. Simple erythematous or vesicular stomatitis may occur with edema and ulceration of the tongue in severe cases. Gold stomatitis has been seen to precede rashes.[1038] Clinically and histologically typical oral lichen planus almost always without accompanying cutaneous lichen planus has been noticed relatively often[874, 833 1039] as a sequel of gold intolerance. The lesions are white irregular thin or slightly

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[1031] Gougerot, Vial and Nakam Lichen ou prurigo verruqueux intense et très étendu, Bull. Soc franç de dermat et syph 43 1582-1585 1936.

[1032] Mary A Horowitz A and Soullard, J Pigmentation en nappes et acné cornée consécutives à une érythrodermie aurique Bull Soc franç de dermat et syph, 40: 1616-1619 1933

[1033] Irgang S Keratoderma and Melanoderma Accompanying Therapy With Gold Compound, Arch Derma & Syph 34 624-629 1936

[1034] Koch A G Chrysiasis, Arch f Dermat Syph 178 323-330, 1938.

[1035] Schmid O E L Chrysiasis, Arch Dermat & Syph 44 446-452 1941

[1036] Lorenzen, J N Ueber das Auftreten von Chrysiasis bei früher mit Natriumaurothiosulfa behandelten Lungentuberkulösen, Beitr Klin d Tuberk 76 696-806, 1931

[1037] Roxburgh, A C Page, A P M and Gordon D Gold Dermatitis With Hyperkeratosis, Brit J Dermat 48: 137 142 1936

[1038] Fournier L and Boltanski E Gold Dermatitis, Rev d stomatol 29 641-646 1930; Ibid. 23 679

[1039] Flinderud C W Lupus erythematodes der Mundschleimhaut, Arch f Dermat. Syph 169 210-222 1935

[1040] Mohrmann, B H U Lichen planus der Mundschleimhaut nach Goldbehandlung Dermat Wchnschr 99 1373-1376 1934

papular keratoses of the buccal and labial mucosae.[illegible] They may disappear after discontinuation of the gold treatment.

A peculiarity of gold is its activating effect on chronic inflammations and infections, especially tuberculous foci. The appearance of papulonecrotic tuberculosis under gold treatment has been reported (Medina after Throne et al.[illegible])

Silver

While there is little known about acute toxidermia caused by silver this metal is more likely to cause permanent deposits and discolorations than any other metal The *dyschromia* from silver is called *argyria* argyriasis or argyrism.

Occupational argyria has been seen in the chemical industry and among workers who blow a silver nitrate solution into glass beads or Christmas tree decorations to silver the inner surface. After many years in this trade such craftsmen sometimes become deep black with a metallic sheen [illegible] Of much greater importance, though rarely reaching the same degree of discoloration is the argyria caused by the use of silver compounds in medical therapy

Silver nitrate pills for peptic ulcer tabes or epilepsy have gone out of fashion but the prolonged use of silver nitrate mild silver protein or colloidal silver in nose drops[illegible] oral sprays or paints, and in genitourinary douches or instillations have produced a great number of cases of generalized argyria Some cases were observed after injections of silver arsphenamines now obsolete.[illegible] Gaul and Staud [illegible] state that after the injection of a total of 8 Gm. of silver arsphenamine argyria becomes clinically apparent.

The first darkening of the skin may appear as early as six months or as late as fifteen years after the initial use of the silver drug but two to three years have been found as the average in 68 cases of the Mayo Clinic [illegible]

It is remarkable that women outnumbered the males 7:4 in this series.

Argyria appears as a slate to bluish gray sometimes bronzed [illegible] rarely black diffuse discoloration predominantly of the skin exposed to light. [illegible] Thus the forehead face neck and the dorsa of the hands are the main sites of the trouble but in severe cases the entire body surface may be involved The conjunctivae may be stippled and the caruncles of the inner canthi the gums and the palate have often been found slate colored

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[illegible] Lortat-Jacob and Legrain, P Lupus érythémateux rasé par l'or Apparition d'un lichen plan buccal intense. Bull. Soc franç d dermat et syph 38 786-787 1931.

[illegible] Throne D Kingsbury J and Myers, C N Unusual Clinical Manifestation Following Intravenous Administration of Gold Compounds, Arch Dermat. and Syph 25 494-507 1932

[illegible] Teleky L Gewerbliche Argyrie, Zbl. f Gewerbehyg. 3 129-133, 1 13

[illegible] Harker J M and Hunter D Argyria, Brit. J Dermat 47 441 1935

[illegible] Wood and M R Argyria From the Use of Colloidal Silver Iodid Intranasally Am J Dis Child 46 1048-1049 1933

[illegible] Spiegel L A Discoloration of the Skin and Mucous Membranes Resembling Argyria Following the Use of Bismuth and Silver Arsphenamine Arch. Dermat & Syph 23 266-248 193

[illegible] Gaul, L. E and Staud. A H Clinical Spectroscopy Seventy Cases of Generalized Argyrosis. J A M A 104 1387 1390, 935

[illegible] Hill, W R., and Montgomery H Argyria With Special Reference Cutaneous History Arch Derma & Syph. 44 588-599 1941

[illegible] Beinhauer Argyria, Arch. Dermat & Syph. 21 708, 1930

[illegible] Stillians, A. W Argyria, Arch Dermat & Syph. 35 67 77 937

large flat papules which have a tendency to coalesce into large plaques of the lichen corneus type.[1081]

There are two kinds of skin *discoloration* known to follow the administration of gold. One is caused by deposits of *melanin* in the upper cutis. This type corresponds to the more common arsenical melanosis and is reversible. It frequently develops after gold rashes [1082] but it may also be primary and occur after small doses.[1083]

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The darkening is diffuse and slate to graphite gray in color Most observers *emphasize a bluish or purplish hue* [1085] *The dyschromia seems to be permanent.* Lorenzen[1086] found that none of his tuberculous patients who had received more than a total of 0 15 Gm of sodium aurothiosulfate per kg body weight escaped chrysiasis but none of those with a total of less than 0 05 Gm per kg developed it. The trouble becomes visible one to three years after the treatment. Mild cases of *chrysiasis* as this discoloration caused by gold deposits is called do not as a rule constitute a very conspicuous disfigurement.

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Hyperkeratoses and diffuse keratoderma after gold treatment are very rare.[1083,1087]

Oral symptoms of gold eruptions have frequently been described Dryness and metallic taste are often the first symptoms of gold intolerance Simple erythematous or vesicular stomatitis may occur with edema and ulceration of the tongue in severe cases. Gold stomatitis has been seen to precede rashes [1088] Clinically and histologically typical oral lichen planus almost always without accompanying cutaneous lichen planus, has been noticed relatively often[874,1089,1090] as a sequel of gold intolerance. The lesions are white irregular thin or slightly

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[1081] Gougerot, Vial and Nekam Lichen ou prurigo verruqueux intense et très étendu Bull. Soc franç de dermat et syph 43 1583-1585, 1936

[1082] Hénry A Horowitz, A and Soullard, J Pigmentation en nappes et acné cornée consécutives à une érythrodermie aurique, Bull Soc franç d dermat. et syph. 40 1616-1619 1933.

[1083] Irgang S Keratoderma and Melanoderma Accompanying Therapy With Gold Compound Arch Dermat & Syph 34 624-629 1936

[1084] Kochs A G Chrysiasis, Arch f Dermat u Syph, 170 323-330 1934

[1085] Schmidt O E L Chrysiasis, Arch Dermat & Syph 44 446-452 1941

[1086] Lorenzen, J N Ueber das Auftreten von Chrysiasis bei früher mit Natriumaurothiosulfat behandelten Lungen tuberk kranken, Beitr Klin d Tuberk 78 686-698 1931.

[1087] Roxburgh, A C Page, A P M and Gordon, D Gold Dermatitis With Hyperkeratosis, Brit. J Dermat 48 137 142, 1936

[1088] Fournier L and Boltanski, E Gold Dermatitis Rev de stomat 38 651-656, 1936 Zbl. 53 679

[1089] Fasserud C W Lupus érythematodes der Mundschleimhaut Arch f. Dermat. u Syph 148 318-322 1925

[1090] Mohrmann B H U Lichen planus der Mundschleimhaut nach Goldbehandlung, Dermat. Wchnschr 99 1373-1376 1934

of argyria but fails to do so in other metallic discolorations e g that caused by bismuth This method of treatment has not yet found general acceptance mainly because it is quite painful [1641] Argyria is an almost permanent trouble. Only occasionally has spontaneous, usually incomplete regression been reported.

Lead

The skin in lead poisoning is said to be sallow and dry often itchy Erythemas pustular eruptions and petechiae occur [1642] The workers who have symptoms of lead poisoning show an incidence of dermatoses mostly dermatitis, which is about three times larger than among the workers in the same industry without symptoms of saturnism The incidence is particularly high in the group with gastrointestinal disturbances. *Hematoporphyrinemia* which is common in chronic lead poisoning is a factor in the pathogenesis of these dermatoses.[1643, 1644] However actual sensitization of the skin to lead is very rare. [1645] In rare instances metallic pigmentations have been seen The well known *gum line* is a deposit of black lead sulfide produced by the hydrogen sulfide which develops in the tartar The line is blue black or gray and follows the edge of the gums. The removable deposits on the border of the gums may also be discolored

Dystrophy and even loss of the nails from lead is known Pain in the nails may indicate nervous disturbances. [1646]

Bismuth

Bismuth may although very rarely cause diffuse blue-black *discoloration* of the entire skin which resembles argyria [1647] Circumscribed and in some instances extensive black pigmentations of the lips [1648] vagina [1649] and other mucosal surfaces have been described

These however are rare considering the large number of luetics who have been treated with bismuth without any evidence of such discolorations.

[1642] Perutz A Gewerbliche Schädigung durch Hg, Pb, und Bi In Oppenheim, Rille, Ullmann Schädigungen d Haut durch Beruf und gewerbliche Arbeit, Vol II Leipzig, 1926 Leopold Voss, pp. 161-167

[1643] Fridlyand, I G Rôle of Lead in Certain Dermatoses, Sovet vrach zhur 43 [illegible], 1939

[1644] Oppenheim R Bleiekzem, Sch[illegible] med Wchnschr 63: 277 [illegible], 1933

[1645] Engelhardt W and Meerkamp, W Bleivergiftung, Dermat Wchnschr 103: 254-260, 1936.

[1646] Schwartz L and Tulipan L Occupational Diseases of the Skin, Philadelphia 1939, Lea & Febiger

[1647] Lueth, H Sutton, D C M Mullen, C J and Muehlberger G W Generalized Discoloration of Skin Resembling Argyria Following Prolonged Oral Use of Bismuth. Case of Bismuthia, Arch Int Med 57 1115, 1936.

[1648] Simons, R D Bismuthlineaue Nederl Tijdschr Geneesk pp 713-713 1937 Ibid, 80 404.

[1649] Wiener K Vaginal Melanosis Caused by Bismuth Therapy and Carcinoma of the Cervix Arch Dermat & Syph 42: 23-29 1940.

Pruritus nitritoid crisis[1900] *urticaria morbilliform scarlatiniform pityriasis rosea-like*[1901,1902] or *lupus erythematosus* resembling[1903] eruptions acne[1904] and *exfoliative dermatitis*[1905-1907] have occurred. They are rarer generally less severe and they do not have the importance of the corresponding arsenical phenomena[1908]



Fig. 181 —Blue line at gingival margin from bismuth medication

The only common surface sign of bismuth poisoning is the *blue gum line* which corresponds entirely to the blue line of lead The bismuth line can often be observed during antiluetic treatment especially around bad teeth The line disappears several months after the discontinuation of the treatment Severe

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[1900] Bertin, E and Breton, A Crises nitritoïdes consécutives aux injections de bismuth, *Paris méd* 2I 476-477 1932

[1901] de Wolf, H F Dermatitis Medicamentosa Bismuth, *Arch Dermat & Syph* 20 [illegible] 1929

[1902] Fox H Generalized Pigmentation and Dermatitis Following Bismuth Therapy Arch Dermat, & Syph [illegible] 1937

[1903] Petges, G and Petges, A Accident cutanés, non-signalés encore, au cours du traitement bismuthiques [illegible] Lésions erythroesquameuses à extension centrifuge simulant le lupus érythémateux [illegible] Rapp Congr Dermatologistes Langue franç 1935, pp 242 244

[1904] Thiel E [illegible] di un raro accidente della terapia bismutica Acne da bismuto, Boll sez reg Soc Ital Derma 3 25 251, 1935

[1905] Touraine [illegible] Racouchot J and Roudet I [illegible] bismuth, [illegible] hyperthermie, dermatite [illegible] albuminurie et polynévrite Bull Soc franç de dermat et syph, 41 [illegible]-573 1937

[1906] Baumann Dermat Zbl [illegible] 40 [illegible] 1931

[1907] Nicolas J Rousset J and Thomassert A Erythrodermie important au cours d un traitement par l hydroxyd de bismuth Bull Soc franç d dermat et syph 41 [illegible] 1937
Roederer J Erythrodermies bismuthiques chez une syphilitique [illegible] erythrodermie arsénicale [illegible] dermat pp 240-243 1931 Zbl 41 450

[1908] Jadassohn F Die Neben [illegible] der Wismut behandlung Handb d H u Gk 18 442-499, 1928.

ulcerative[illegible] even fatal[illegible] stomatitis or glossitis may also develop but this is much rarer than in mercury poisoning

Mercury

It has almost been forgotten that mercury is able to produce the same types of *rashes* which occur due to arsenic, gold bismuth and other metals. Urticaria follicular and diffuse erythema morbilliform scarlatiniform and papular rashes and also exfoliative[illegible] dermatitis are known. However they are less common and also less dangerous than the corresponding arsenical dermatoses. Macular rashes resembling erythema infectiosum were established as mercury eruptions due to the administration of calomel and the filling of dental cavities with amalgam [illegible] The rashes are often the only symptom of mercury intoxication[illegible] Scaling and diffuse or reticular hyperpigmentation may follow the erythroderma [illegible]

The most important surface symptom of mercurial poisoning is *stomatitis* Almkvist,[illegible] who has devoted so much effort to the study of mercury poisoning suggested that H_2S which develops in the decomposition of proteins under the gums and in inaccessible pockets of the oral mucosa, forms HgS with the mercury carried by the bloodstream He also found that mercury sulfide is more irritant to the oral mucosa than other metal sulfides. The first deposits of HgS are found in the loops of the capillaries of the papillae.

The first clinical symptoms are usually salivation metallic taste and a feeling of excessively long or dull teeth Soon the gums start to swell and form pockets between themselves and the teeth in which pus is retained permitting prolonged contact of H_2S with the circulating mercury

The inner lining of these pockets is the first site of superficial necrosis. From there the stomatitis which is soon complicated by infection spreads to the open surfaces of the gums where pseudo-membranes and ulcers quickly form if the process is not halted by treatment and discontinuation of the mercury In severe cases, the entire mouth may become affected the tongue edematous the tonsils ulcerated the teeth loose and even pneumonia and fatal sepsis have in the days of the mercurial therapy of syphilis occasionally occurred [illegible]

Treatment consists of cleaning and disinfecting the pockets with thin pointed cotton applicators dipped in strong silver nitrate tincture of iodine or any other strong astringent and disinfectant. Naturally the teeth should be kept meticulously clean and another drug should be substituted for the mercury preferably the nonmetal penicillin

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[illegible] Mi tras Stomatitis ulcerosa et necroticans bismutica, Zbl 80 441

[illegible] Beerman H Fatalities Due to Bismuth in the Treatment of Syphilis, Arch Dermat & Syph. 28: 797-801, 1933

[illegible] Almkvist, J Quecksilberschädigungen, Handb d H. u. G. Ok 18 178-232, 1928.

[illegible] Jenny E Ueber Quecksilberexanthema bei Kindern, Schweiz med. Wchnschr 60: 943-944, 1930

[illegible] Gougerot, P Blum, J Bralez and Archambaud, R Pigmentation réticulée unique près érythrodermie hydrargyrique Arch dermat.-syph Hôp St Louis 4 306-37 1932

[illegible] Picard M., Maurel, G and Temerson Stomatite mercurielle gangréneuse mortelle, Bull Soc. franç. de dermat et syph. 43 1503-1505, 1936.

Aluminum

Urticaria dermatitis pruritus herpes spider nevi pernlones, brittleness and longitudinal lines of the nails and paronychia are the skin manifestations of a syndrome which Spira[1667] believes to be caused by chronic aluminum poisoning

Thallium

Thallium is a heavy metal which can produce all the toxic effects of this group Sufficient doses cause severe pains in the limbs, especially in the knees salivation stomatitis gastrointestinal and liver symptoms nephritis cystitis, peripheral neuritis and disturbances of the central nervous vegetative and endocrine systems.[1668-1671]

Dermadromes.—A peculiar affinity for the *hair* causes shedding of the head hair by doses which do not cause other toxic symptoms. It is still controversial whether this effect on the hair is due to local damage[1671] or whether it is evidence of an elective disturbance of the endocrine sympathetic system [1668]

Thallium acetate has been for its effect on the hair widely used in the treatment of tinea of children

If 6 to 8 mg of thallium acetate per kilogram body weight is given in one dose the hair starts to fall after one week and complete baldness of the head is reached after nineteen days.*[1672]

The eyebrows especially the mesial portion the eye lashes the lanugo the pubic and axillary hair and in experimental rats the whiskers, prove more but not entirely resistant [1673] The epilation of the scalp is occasionally spotty After 3 to 4 weeks the hair starts to grow again and reaches its old vigor after 2 to 3 months This amazing treatment has however been largely abandoned because of a number of fatal poisonings which have occurred either by over dosage or by administration to adult patients or though very rarely in spite of all precautions [1666] Hypohidrosis is one of the sympathetic effects of thallium Other dermadromes of thallium poisoning are rare They include urticarial erythematous macular and lichen planus-like exanthems After severe single dose poisonings which have frequently been caused by the ingestion of roden ticides containing thallium salts white transversal nail bands comparable to

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*There is consensus [illegible] only children up [illegible] 10 years should be treated [illegible] thallium The per kilogram doses which are rela[illegible] harmless [illegible] children prove highly [illegible]

[1667] Spira L The Clinical Aspect of [illegible] Poisoning by Aluminum [illegible] London, 1933 John Bale Sons & Danielsson Ltd

[1668] Karrenberg [illegible] L Nebenerscheinungen nach therapeutischer Verabfolgung von Thallium. Zbl 42 1 31 1932 [illegible]

[1669] Buschke A and Peiser B Die biologischen Wirkungen und die praktische Bedeutung des Thalliums Ergebn d allg Path [illegible] path Ana 25 1-47 [illegible]

[1670] Buschke A and Peiser B Ergebnisse der Thalliumforschung und ihre praktische Bedeutung [illegible] Klin Wchnschr 11 [illegible]-1251 [illegible] [illegible]

[1671] Truffi G Azione biologica dell acetato di Tallio Arch d sc biol 13 371-419 1929

[1672] Galewsky E Erkrankungen der Haare und des Haarbodens Handb d H [illegible] Gk 13 1 [illegible]-[illegible], 1932

[1673] Keel Thalliumvergiftung Zbl 41 [illegible] [illegible]

[1666] Philadelphy A Hauterscheinungen durch Thallium. Dermat W[illegible] [illegible] 78-80 1931

Mees's bands in arsenic poisoning have been described [illegible] and thallium has been found in the nails.[illegible] The local application of salve containing thallium acetate for the purpose of epilation has proved effective but has resulted in a great number of systemic poisonings.

Carbon Monoxide

Carbon monoxide poisoning rarely causes skin manifestations. Shillito Drinker and Shaughnessy [illegible] did not mention any skin damages in their survey of 21 143 cases, but it seems that this report did not pay enough attention to the cutaneous symptoms.



Fig. 18[illegible].—Localized gangrene following carbon monoxide poisoning. (From Seifert, E. A. J. M. Soc. New Jersey.)

The cherry red lips and deep *cyanosis* of persons poisoned with monoxide gas is generally well known. Local *edema* of the extremities was known to the older observers. It may be related to the *circumscribed necroses* found after severe gas poisonings.[illegible] The lesions start as serous or hemorrhagic bullae which

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[illegible] Adler, A. Nagelveränderung bei Thalliumvergiftung, Dermat. Ztschr. 63: 290-291, 1932.

[illegible] Wilkes, W. Fall von akuter Thalliumvergiftung, Ibid. 82: 193, 1934.

[illegible] Shillito, F. H., Drinker, C. and Shaughnessy, T. J. The Problem of Nervous and Mental Sequelae in Carbon Monoxide Poisoning, J. A. M. A. 106: 669, 1936.

[illegible] Bernstein. Hautnekrose bei Kohlenoxydvergiftung, Ibid. 46: 626, 1932.

[illegible] Oppenheim, G. *Umschriebene Hautgangrän und Purpura nach Leuchtgasvergiftung*, Ibid. 42: 161, 1933.

[illegible] Seifert, E. A. Factors in Peripheral Skin Lesions *Following* Carbon Monoxide Poisoning, J. M. Soc. New Jersey 40: 418–420, 1943.

develop into deep sharply outlined round ulcers or patches of dry gangrene. Such necroses have been seen on the heels soles, ankles, calfs sacral area fingers and scalp In several cases an entire limb was affected [illegible]

Perhaps decubitus is at least in some cases a factor in the pathogenesis of the ulcers but there are clinical and histological reasons to blame primary vascular damage instead

Herpes zoster especially of the forehead is considered to be a characteristic sequel of monoxide poisoning[illegible] (Schas in discussion to Fischel [illegible])

Sedatives

The *barbiturates* quite frequently produce *rashes* of allergic character Pruritus and urticarial macular scarlatiniform multiform or petechial exanthems are fairly common and well known especially from phenobarbital Bullous eruptions in the mouth have also been observed [illegible] The severe and in some instances fatal cases of exfoliative dermatitis are fortunately very rare.[illegible]

Nirvanol is a hypnotic which almost constantly produces a morbilliform *exanthem* after 6 to 14 days of regular administration The rash is accompanied by conjunctivitis stomatitis and other mucosal reactions fever cyanosis dizziness and other nervous symptoms, gastrointestinal and hepatic symptoms and albuminuria a syndrome which is known as *nirvanol disease* (V Pfaundler after R. L. Mayer[illegible]) Nirvanol is used in the treatment of chorea The therapeutic result depends on the development of the nirvanol allergy [illegible]

Bromine

Morbilliform urticarial bullous vesicular vacciniform and other *rashes* are occasionally seen after the administration of bromides. More characteristic are acneiform eruptions which appear at the predilection sites of acne vulgaris especially on and around the nose It seems that bromine acne is more apt to suppurate and to form flaccid pustules than the common juvenile form [illegible]

In some cases *ulcers* form which by central healing and partial peripheral advance may resemble tertiary syphilis A peculiar feature of some bromine reactions is the tendency to develop *tuberous* or tumor like vegetations These bromodermas are known in several varieties and combinations. They occur as papillomatous confluent crustous suppurative or ulcerating sessile or tuberous usually painful eruptions. Small subepidermal abscesses in the edges of the lesions may create a blastomycosis-like picture After the expression of pus from large lesions a quite characteristic cribriform surface results [illegible]

[illegible] Earer N and Spilberg S Gangrene of Lower Extremity Following Carbon Monoxide Asphyxia, Am J Clin Path. 10 111 120 1940

[illegible] Drinker C K Carbon Monoxide Asphyxia, New York, 1938 Oxford University Press

[illegible] Knapp A Seltene Fälle an Herpes Zoster München med Wchnschr 87 [illegible] 1940

[illegible] Fischel 3 Fälle von Haut erkrankungen bei Leuchtgasvergiftung, [illegible] 1 107 1931

[illegible] Hoffman M Phenobarbital Eruption of the Mouth, Arch Dermat & Syph 25 [illegible], 1932.

[illegible] Jadassohn K Ueber Barbitursäure-Allergie Med Klin 29 189-191 1933

[illegible] Madden J F Nirvanol Eruptions Arch Dermat & Syph 28 1065-1073 1933

[illegible] Kiessling, L. Toxicodermien, Handb d. H u. Gk 4 2 232-376 1933

[illegible] Netherton E W Nodular Papillomatous Bromoderma, Cleveland Clin. Quart. 12 [illegible], 1945.

The bromodermas are most often seen on the lower legs and vary widely in size and number of lesions. There may be a few or several hundred and some may be as small as peas while others may reach the size of a fist.[illegible] The various types of lesions may be seen in the same patient at the same time. A characteristic foul odor may be present.[illegible]

The lesions have occasionally been first observed several months after the ingestion of bromine had been discontinued. Bromoderma sometimes develops out of other pre-existing skin lesions e.g ulcers scars and injuries. The tongue and other parts of the mouth may participate in the fungating process.

The *allergic* character of the bromodermas has been recognized by most authorities but is disputed by some investigators [illegible] mainly because of negative skin tests.



Fig. 156 —Acneiform eruption from bromine.

The positive transfer of the allergy to the guinea pig has occasionally been demonstrated [illegible] Bloch and Tenchio[illegible] elicited in their case of severe bromoderma with fatal outcome positive patch tests after 24 hours. Later these reactions turned into bromoderma an interesting demonstration of Koebner's phenomenon [illegible] Positive scratch and intradermal tests have also been elicited [illegible] Excessive eosinophilia is another argument in favor of the allergic nature of the bromodermas The vegetations have several times been found to be free of bromine The diagnosis of the bromine dermatoses has to consider such heterogenous diseases as the acute exanthems, acne vulgaris syphilis blastomycosis epithelioma mycosis fungoides, erythema nodosum and others.

[illegible] Lehner E. Bromoderma, Klin. [illegible] 228, 1936.
[illegible] Soreka, E. I Bromoderma Vegetans, Vestnik. f. dermat. [illegible] 1931
[illegible] Bloch, B and Tenchio, F Bromoderma Vegetans Arch f Dermat Syph. 165 [illegible]-148, 1932.
[illegible] Hamann, K Bromoderma und Hautallergie, Arch. f. Kinderh. 110: 103-107 1937
[illegible] Bernhardt, R. Acne bromata provocata, Arch. f. Dermat. u. Syph. 171 113-114 1934.



Fig. 157.—Bromoderma tuberosum (From Netherton, E. W. Cleveland Clin. Quart.)

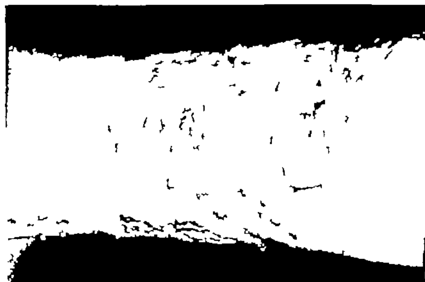


Fig. 158.—Bromoderma tuberosum (From Netherton, E. W. Cleveland Clin. Quart.)

The copper or brownish hue of the bromodermas is often emphasized

Discontinuation of the bromides and large amounts of fluid and sodium chloride[1094] are important in the *treatment.*

The *prognosis* of treated cases is generally favorable if the use of bromides is discontinued. Scarring and pigmentation are common sequelae Rarely the lesions continue to develop despite discontinuation of the drug and treatment. Such cases may end fatally [1095]

Iodine

The eruptions following the internal use of iodine and its compounds follow the pattern of those produced by bromine Acne is the most common dermadrome of iodism Vesicular bullous,[1096] and hemorrhagic eruptions have been seen more often than the vegetating forms. The allergic nature of the iododermas and the sensitizing effect of iodized table salt[1097] has been established by experimental investigations [1098]

Fatal cases of iododerma tuberosum are very rare [1099-1102]

Some Other Drug Eruptions

Almost all drugs and poisons are able to produce allergic skin eruptions. Among the great number of multiform morbilliform, scarlatiniform eczematoid hemorrhagic bullous vesicular and other exanthems a few stand out because of unusual clinical features

Phenolphthalein eruptions are well-defined round or oblong red and later purplish brown spots They sometimes appear as large bullae. The macular lesions are lentil to palm sized and are most often seen about the buttocks and the lower back, but also on the extremities.

The bullae are large and deciduous leaving an erythematous and pigmented base Eczematous forms are less well known The lesions may after an inflammatory stage recede and leave only a faint pigmentation It is a peculiarity of the phenolphthalein eruptions to appear in exactly the same sites, even after complete or almost complete disappearance and after long intervals. This is known as a fixed eruption

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[illegible] Wise L J Further Contributions to the Experimental Aspects of Iodid and Bromid Exanthems, Arch Dermat & Syph 81 407-410, 1933

[1096] Spillmann Weiss and Maison Dermit bulleuse généralisée d origine iodique chez une h'miplégique Bull Soc franç de dermat et syph 40: 1264-1266, 1933.

[1097] Becker P E Iodized Table Salt as an Etiologic Factor in Ioderma, Arch Dermat & Syph. 29 [illegible]-[illegible], 1934.

[1099] Kiechl G Eine seltene Form Jodema [illegible], Jap J Dermat. 33: 130-131 1933 Zbl. 48 82

[1100] Hollander L and Fetterman, G H F tal Ioderma, Arch. Dermat. & Syph. 31 [illegible]-241 1936

[1101] Herxenberg, H and Moerchhiltzbaum, L Ueber Thromboangiitis obliterans (Beitrag z. Pa hogenese des Ioderma bullosum vegetans) Beitr path Ana allg. Path. 94 [illegible]-[illegible], 1934.

[1102] Eller J J and Fox, E C Fatal Iododerma, Arch Dermat & Syph. 24 743-757 1931.

Phenolphthalein is an ingredient of more than a hundred proprietary laxatives.[1162] Similar fixed eruptions also occur as a reaction to *antipyrin*.[1163] The eruption to either drug may develop within an hour after ingestion. Severe melanoderma after phenolphthalein is very rare.[1164]

Sedormid, a mild sedative of the urea group, has in many cases caused severe thrombocytopenic purpura.[1165, 1167]

Veramon, a popular European combination of barbital and amidopyrin, may give rise to fixed symmetrical eczematous patches and mucosal swellings. Its use has been discouraged because of the danger of *agranulocytosis* from the amidopyrin content.

Quinine eruptions are most often scarlatiniform. In severe cases exfoliative dermatitis may develop. Severe purpura is a rare event. About one out of 200 patients is or becomes allergic to quinine.[1168]

Atabrine, which proved to be a satisfactory substitute for quinine, may cause a lemon to sickly greenish yellow discoloration[1169] after one to four months of use. The yellow dyschromia is uneven. In contrast to icterus, with the heaviest discoloration on the exposed parts and in the folds of the body. The sclerae remain white. The extensor[861] surfaces of the arms and feet, the webs, the nape, the forehead and the circumoral area are most deeply stained. A "golden ring" around the mouth is a peculiarity of the atabrine pigmentation. Unlike the discoloration in carotinemia, the palms are less yellow than the dorsa of the hands.

Bluish pigmentations have been seen in the hard palate, epiglottis, tracheal rings, and the nail beds.

During the war in the South Pacific, especially in New Guinea, many cases of a dermatosis with features both of an *atypical lichen planus and eczematoid dermatitis* occurred among the troops who took atabrine regularly for the suppression of malaria, but it is not generally recognized that atabrine is the cause.[111] The condition is characterized by various combinations[11] of purplish hypertrophic lichenoid papules and plaques, frequently with a rough, verrucous surface, and eczematoid plaques in all stages of erythema, oozing and scaling.

[1162] Belot, O. H. and Whitney, H. A. K.: Phenolphthalein Compounds, Arch. Dermat. & Syph. 36: 279-281, 1937.

[1163] Basch, G. and Saiston, J.: Plaque érythémato-pigmentée fix et éléments bulleux à type érythème polimorphe par ingestion d'cachets à base d'antipyrine, Bull. Soc. franç. d. dermat. et syph. 42: 453-455, 1935.

[1164] Weiss, R. S.: Dermatitis Medicamentosa (Phenolphthalein), Arch. Dermat. & Syph. 23: 1182, 1931.

[1165] Falconer, E. N. and Schumacher, J. C.: Purpura Hemorrhagica Due to Ingestion of Sedormid (Allyl-isopropyl-acetyl-carbamide), Arch. Int. Med. 65: 123-137, 1940.

[1166] Loewy, F. E.: Thrombopenic Hemorrhagic Purpura Due to Sedormid. Allergotoxic Effect, Lancet 1934, 1: 845-846.

[1167] Huber, H.: Case of Purpura Hemorrhagica Resulting From Sedormid, J.A.M.A. 113: 674-675, 1939.

[1168] Hauer, A.: Ueber Chininintoxikation und Chininidiosynkrasie, Deutsche med. Wchnschr. 61: 333-336, 1935.

[1169] Schechter, A. J. and Taylor, H. M.: Atabrine Pigmentation, Am. J. M. Sc. 192: 645-650, 1936.

[1170] Epstein, E.: Lichen Planus-Eczematoid Dermatitis Complex of Southwest Pacific, Bull. U. S. Army M. Dept. 5: 657-663, 1945.

[1171] Leonard: Reactions Attributed to Atabrine (Atypical Lichen Planus), J.A.M.A. 129: 1091-1093, 1945.

The dermatosis may also though rarely consist of lichenoid elements alone. More frequently the eczematoid lesions dominate the picture entirely even to the extent of severe generalized *exfoliative dermatitis*

The legs and forearms, the dorsal surfaces of the hands and feet and the face neck buttocks and genitalia are predominantly and symmetrically affected Atrophy and hyperpigmentation, nail changes, and shedding of the nails patchy alopecia and dyshidrosis have been described as late sequelae.

With the exception of severe exfoliative dermatitis, the course is generally benign if atabrine is discontinued.

Picric acid may cause generalized *yellow discolorations* which simulate icterus. The sclerae take part in the staining

The *sulfonamides* may cause a great variety of eruptions which are essentially the same as those due to the barbiturates the arsphenamines and many other drugs A special feature is the frequent *photo-sensitization* caused by the use of sulfonamides

Ephedrine besides occasionally causing generalized erythemas and dermatitis has, in some persons, a tendency to produce urticaria and local swellings, especially of the eyelids. [11-11]

Codeine rashes [114] have been described as follicular erythemas which quickly develop into scarlatina like exanthems. Codeine and opium occasionally produce pruritus or formication.[1 15] Paresthesias are also a dominant symptom in chronic *ergotism* from[117] Claviceps purpurea infected rye and wheat and in ustilaginism from corn infected with Ustilago maydis.[118] Even acrodynia like cases of morbus cerealis have become known. In *favism* a severe poisoning occasionally caused by the eating of broad beans (vicia faba) purpura is an important symptom [119]

Dinitrophenol the dangerous weight reduction agent caused urticarial macular maculo-papular and eczematoid rashes in 7 to 20 per cent of the treated persons. [120 121] The frequent *yellow discoloration* is due to the staining and is not caused by icterus [120 122]

[illegible] Dallen, S S Francis, K and Parker J M. Dermatitis Medicamentosa, Due to Ephedrine J Allergy 3 453-458, 1932

[illegible] Ayres, S J and Anderson, N P Dermatitis Medicamentosa Due to Ephedrine, J.A.M.A. 97 437-440, 442-443 1931

[illegible] Abramowitz, E W and Noun M H Ephedrine Dermatoses, Brit J Dermat 45 235-237 1933

[illegible] Scheer M and Keil, H The Skin Eruptions of Codeine, J A M.A. 102: 908-910 1934

[illegible] Goldsmith, W N Significance and Treatment of Itching, Practitioner 143: 38-44 1939

[illegible] Kamdita, J Chronic Endemic Ergotism Its Relation to the Vasomotor and Trophic Diseases, Arch J Med 47 540-564 1931.

[illegible] Mayerhofer E [illegible], eine bisher unbekannte Form alimentärer Störung bei der Maisernährung im Kindesalter Med Progr 6 133-137 1931 Zbl. 39 778.

[illegible] Jimenez-Diaz, C and Fiel, O M Anaphylactic Purpura Due t Sensitization Beans (Purpuric Form of Favism) Rev clin espan 5 179-180, 1942.

[illegible] Frumess, G M. Allergic Reaction to Dinitrophenol (Case J A.M A 102: 1219-1220 1934

[illegible] Kerten B M Dermatitis Medicamentosa Formula 281 (Dinitrophenol) Arch Dermat & Syph 31 373-375 1935

[illegible] Simkins Dinitrophenol and Desiccated Thyroid in Treatment of Obesity J A M A 108 2110-2117 (2193 2 99) 1937

CHAPTER XIV

DISORDERS OF THE CIRCULATION

Heart Disease

Cardiac decompensation no matter what its cause may be produces a rather uniform syndrome with dyspnea cough palpitation and precordial distress dominating the complaints. Cyanosis and edema are almost always present

Cardiac Decompensation —*Cyanosis* is not only caused by the deficient blood circulation If the state of decompensation lasts for some time the respiratory system suffers and the oxygenation of the venous blood becomes insufficient increasing the cyanosis Cyanosis is an early sign of valvular heart disease especially of the right heart but also though later of the mitral valves It is less pronounced in aortic insufficiency [illegible]

Extreme degrees of cyanosis are encountered in the *newborn* infant with congenital affections of the heart. In contrast to the cyanosis in acquired and adult types of heart disease the blue discoloration may cover the entire body *surface of the baby (Morbus caeruleus) In later life the cyanosis is usually* restricted to or at least most marked in the acra. The cheeks the lips the nose the ear lobes the finger tips, the toes the elbows and the patellae are chiefly affected [18] Frequently only a slightly purplish hue of a seemingly healthy complexion indicates an underlying cardiac insufficiency The cyanotic parts especially the feet and lower legs are cool

If cyanosis exists for a longer period sharply drawn *telangiectases* appear On the face they resemble rosacea or they are the first stage of rosacea Telangiectases occur also on other parts of chronically congested skin e g between the shoulder blades and on the abdomen [illegible]

Edema usually is seen first in the skin about the ankles but later it may involve the entire skin and the subcutaneous tissues Chronic congestion may cause *clubbing* of the fingers and toes more so in children than in adults.[illegible]

The skin in chronic congestion is if not yet cyanotic, *pale* and often grayish Slight *hemorrhagic* tendencies are an early sign of decompensation though they may be only detected by the tourniquet test or the capillaroscope [illegible] Naegeli mentions extravasations over the thorax and epigastrium in decompensated mitral insufficiency

The *pallor* of the patients with mitral stenosis before the cyanosis occurs *is marked*

Hyperpigmentation occurs—especially in children—on the forearms and the dorsa of the hands and fingers. The pigment is hemosiderin from the extravasa

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[illegible] Bechel H Chronische und akuten beim Kinde Monatschr f Kinderh 46 [illegible] 1929.
[illegible] Jürgensen E Okkult Hautblutungen, Deutsches Arch. f klin Med 170 [illegible] 1931

tion [illegible] Slight *jaundice* is frequent. It appears less pronounced in the edematous parts.[illegible] Increased *freckles* are often seen in juveniles with decompensated mitral insufficiency.[illegible]

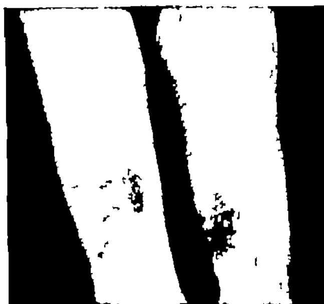


Fig. 180.—Myocarditis. Dermatitis of legs, exacerbating and receding with cardiac decompensation.



Fig. 181.—Dermatitis of the legs in hypertension. Parallelism of exacerbations with degree of cardiac decompensation.

[illegible] Kaufmann, E.: Die pathologischen Pigmentierungen der Haut. Handb. d. H. u. Gk. 4/2, 1911 1221 1933

Hypertrichosis is a symptom of chronic congestion in children The back, the face, and the extensor aspects of the extremities exhibit the increased lanugo most distinctly [1133]

Eczema of the lower legs, sometimes with a purpuric component is an occasional accompaniment of decompensation The healing with improvement of the circulation and relapse on recurrence of decompensation is proof of the circulatory factor in these eczemas

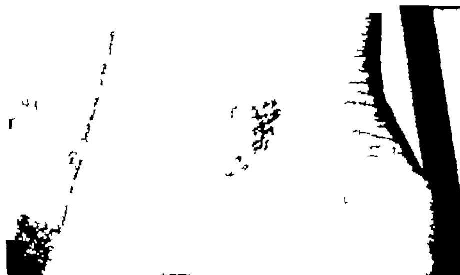


Fig. 161.—Schamberg's dermatosis in circulatory stasis (Courtesy Dr M Jessner)

The *pulsating erythema* of the nail bed or of a dermographic line known as the capillary pulse is a well known sign encountered in aortic insufficiency but also in other conditions. The jerking pulsation can be demonstrated in the capillaroscope. [1135]

Arteriosclerosis, Hypertension

Arteriosclerosis affects the arteries of the skin[1137] as well as those of other organs (see Chapter on Old Age) The capillaries appear tortuous and thin in the capillaroscope (E. Weiss after B Niekau[1136])

The clinical skin changes produced by arteriosclerosis are best observed in the *feet* [1138] The skin is dry due to the impairment of the glandular functions. The nails become atrophic and brittle or thick. Corns and calluses become thicker The lanugo hair on the dorsa of the phalanges disappears. The foot including the sole may become cyanotic on dependence and pale on elevation

[1136] Niekau B Kapillarbeobacht ungen an der Körperoberfläche des Menschen, Ergebn d. inn. Med u. Kinderh 22 479-551 1922

[1137] Wiedmann, A Beiträge zur Pathologie der Gefässerkrankungen der H t III Mitt. Die Arteriosklerose der Haut Dermat Wchnschr 102 69-75, 1936.

[1138] Nomland R Cutaneous Manifestations of the Circulatory Disorders of the Foot J A M A 124 747 750 1944

Nomland[1127] believes that the more nearly horizontal the leg is when pink color returns the greater is the insufficiency of the arterial supply. Wounds and infections, even trivial ones, heal slowly and may cause severe complications. This is the more important since *pruritus* is a common symptom of cutaneous arteriosclerosis and decompensation.[1128]

Cardiac infarction may leave its mark in cross furrows of the *nails* (Beau's lines) or more rarely in transversal white lines.[1129] Cross furrows have also been observed on the toenails in intermittent claudication.[1130] Occasionally an *erythema* of the face and neck resembling erythema pudoris has been seen in *angina pectoris*[1132] and *hypertension*.[1131]

Herpes Zoster intercostalis has often been related to angina pectoris.[13,1133]

The most important though by no means constant cutaneous manifestation of hypertension is *pruritus*. It is often severe and reflects in its intensity the ups and downs of the blood pressure. Severe attacks of pruritus may precede apoplectic episodes. Rarer than pruritus alone are *eczematous* or *pruriginous* changes. It is in such cases hard to decide whether the dermatosis is due to hypertension, nephrosis or decompensation since it may accompany all of these conditions. The eczema sometimes seems secondary to prurigo, the itching papulourticarial lesions of which are quickly destroyed by scratching. A slight scab-covered spot of lentil to fingernail size ensues. Groups of such lesions in various stages of development and lichenification are usually found along the legs and in some severe cases over the entire body. These cases are at least temporarily benefited by superficial X-ray therapy.

In obstinate cases of eczema of the hands, of nummular eczema and of scaling and itching of the finger tips one should consider the state of the circulation and treat accordingly.

Hypertension, aortitis, arrhythmia, chronic glomerulo nephritis and other vascular and hepato-splenic disorders may be accompanied by pigmented and depigmented hemorrhagic inflammatory plaques on the lower legs. Favre[86] and his collaborators have stressed the internal relationship of this condition which he called *angiodermatitis pigmentosa purpurica*. He stressed that this common syndrome has nothing to do with varicose veins and that it does not show the features of eczema. The underlying periosteum is often early affected. The patches run a gamut of colors from yellow to blue black. The surroundings are often depigmented. The lesions are also variable in size and contour. Hemorrhagic infiltration with formation of a black scab and ulceration occurs.

[1128] Cohen, G. Pruritus als dyspnoischen Symptom mit Bemerkungen über pruriginöse Sensationen, Arch. f. Derm. Syph. 149: 33, 1925.

[1129] Urbach, E. Wide Cross Striae of the Finger Nails Following Cardiac Infarction, Arch. Dermat. Syph. 51: 106-107, 1945.

[1130] Schlesinger, H. Das Nagelsymptom bei dem intermittierenden Hinken, Med. Klin. 26: 921-922, 1930.

[1131] Pertorais, A. and Flora, G. T. Angine de poitrine d'effort ... érythème initial et poussée hypertensive, Bull. et mém. d. Soc. méd. Hôp. d. Paris 47: 1450-1451, 1931.

[1132] Weber, F. P. Dermatic Blotchy Flushing Over Neck and Upper Thorax in an Elderly Woman With High Blood-Pressure, Proc. Roy. Soc. Med. 28: 731, 1935.

[1133] Severin, J. Herpes zoster bei inneren Organerkrankungen, Deutsche med. Wchnschr. 52: 968-903, 1926.

Tenderness and scaling are other features The pigment is hemosiderin In spite of some similarities the common angiodermatitis is to be separated from Shamberg s disease and from purpura Majocchii. Syphilis is the most common etiologic factor

The compression of the superior vena cava by an *aneurysm* of the ascending aorta may cause congestion and tortuosity of the veins of the neck and face even of almost the entire upper half of the body There is also edema and cyanosis. Pressure on one of the innominate veins produces these signs on one side only usually the left.[13] A leaking aneurysm of the abdominal aorta may cause huge suggillations of the scrotum and lumbar area



Fig 162 Female aged 17 years Arteriovenous aneurysm following fracture of radius Increased growth of the affected hand large pseudohemangiomatous coiled vessels, increased skin temperature hyperidrosis and bruits (Patient of D Karl Schlaepfer)

Peripheral arterio-venous aneurysms are usually caused by trauma They cause hemangioma like accumulations of tortuous blood vessels with pulsation and murmurs The skin over such a lesion is warmer than normal and perspires more readily The increased blood supply causes increased growth of the involved part including the bones

Thrombo-Angiitis Obliterans (Buerger s Disease)

In this disorder of unknown but [136] probably bacterial etiology [137] the peripheral arteries and veins of the legs rarely of the arms—sometimes together with adjacent nerves [138] are affected Arteritis with thrombus formation in single or

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[136] Buerger L The Circulatory Disturbances of the Extremities Philadelphia and London, 1924 W B Saunders Co

[137] Allen, E V Thromboangiitis Obliterans Bull New York Acad Med 18 165-189 1942

[138] Kiaer S Thrombo-Angiitis Obliterans Buerger Acta orthop Scandinav [illegible] 103-122, 1931 Ibid [illegible] 550 1931 1932

multiple foci causes a state of ischemia with severe pain The pain may occur on exertion and then it has the character of intermittent claudication or it may be experienced while the patient is at rest. In this case the pain is continuous, worse at night and sometimes aggravated[1137] and sometimes eased by dependency Gangrene with severe pain may occur The course of the disease is most often chronic and slowly progressive in attacks. The peripheral pulses in the affected limb are absent or diminished. The sufferers are almost exclusively young men (98 per cent) often Hebrews (28 per cent) and heavy cigarette smokers (93 per cent) [1139] Familial incidence has been observed [1140]

Dermadromes —The skin [a] of the toes is at least in the fairly advanced stages, moist, cool often scaly tender and reddish-blue in patches especially if the patient stands. *Elevation* blanches the limb Reactive hyperemia is apt to follow on lowering the leg except in severe cases.[1138] If the time required for the return of color while in the dependent position is longer than 10 seconds impaired arterial circulation exists. In marked impairment of the arterial circulation by thrombo-angiitis the return often takes more than forty-five seconds.[1137] Refilling of veins after emptying by elevation also takes longer than ten seconds. Superficial palpable *phlebitis* is a feature in Buerger's disease which leaves *hemosiderin pigmentation* for a long time after healing

Variable degrees of *pallor or cyanosis* may follow exposure to *cold* or *emotion* [1137] If *gangrene* develops it is less extensive than in arteriosclerosis because of the smaller caliber of the thrombosed arteries. It is usually of the moist type. The endangered toes are bluish especially the nailbeds. The skin is often glossy and atrophic. Subungual keratosis develops frequently Ulceration of the big toe is the commonest form of necrosis. Gangrene of the fingers is much rarer than gangrene of the toes since the establishment of collateral circulation has a better chance in the arms than in the legs. Besides the occlusion by thrombosis vasospasm plays a part The diagnosis has to exclude arteriosclerosis. Here the picture is very similar but the patients are older the pain at rest is milder gangrene is more apt to be dry and phlebitis and edema are not features. Lipemia is frequent in arteriosclerosis and the arteriosclerotic artery may be detected by X-ray [a]

The *treatment* requires complete abandoning of smoking vascular exercise by systematic raising and lowering of the legs, and warm baths. Mechanical pulsating devices do not seem to be very effective in Buerger's disease Amputation nerve section or sympathectomy are often necessary [1137, a]

Shock

Shock is characterized by circulatory failure and deep depression of the nervous functions. It may be caused by trauma hemorrhage massive infection burns intestinal perforation cardiac failure and other conditions.

[1139] Horton, B F Thrombo-Angiitis Obliterans, 919 Cases Incidence of Amputation, Mil. Surgeon 84: 599-600, 1939

[1140] Mészáros, K Arteriitis obliterans (Thrombangiitis Buerger) als familiäre Erkrankung, Deutsches Arch f klin Med 171: 381-396, 1931

[1141] Hermann, H Circulatory Diseases of the Extremities, New York, 1936, The Macmillan Company

In shock the effective circulating blood volume i e cardiac output and venous return is reduced and the peripheral flow of blood is slowed down [118] The blood pressure is at first maintained by vasocompensatory mechanisms but drops as soon as these mechanisms become weak. While in the initial or premonitory stage of shock the pulse may not be altered it becomes rapid and thin in the fully developed syndrome.

Dermadromes.—Di Palma [119] stresses the diagnostic importance of the skin phenomena in the initial phase the knowledge of which may enable the physician to apply help before the onset of deep shock. For the examination the patient has to be stripped and remain exposed to room temperature for at least 10 minutes. If the skin can be blanched by pressing the forefinger forcibly into it some blood must be in the skin The color contrast with the unblanched skin and the rate of fill-in of the blanched areas permit quick though rough and unreliable estimate of the peripheral blood flow Gentle touching with the back of the digits permits the determination of gross differences between the skin temperature of the trunk and the extremities. Such differences would indicate a slow blood circulation in the periphery The color of the skin is an excellent guide in the estimation of the rate of the peripheral blood flow It should be judged by the hue of the cheeks the lips and especially of the nail beds. Di Palma [n] advises the acquisition of competence by observing the nail beds under controlled conditions of circulation produced by a blood pressure cuff and varying elevation of the arm Brick red purplish and finally deep purplish blue indicate the degrees of peripheral circulatory failure

Since the brick red hue is an early sign it is most important. Simultaneous forcible stroking of the skin with a blunt instrument on the chest and on the forearms provides an opportunity to compare the differences between the time of appearance and the color of the red dermographism The peripheral blood flow must be considered slow if the red line appears later than five seconds and if the reaction on the forearm is delayed in comparison with the chest The color should be bright red DiPalma Muss and Foster[120] have devised a method which measures the minimal time required to elicit hyperemia by a weighted rubber ring placed on the skin of the chest and arm (stimulus time) and the time after which the hyperemia fades (clearance time) These times are compared with those obtained from a normal person in the same room

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[119] DiPalma, J R The Circulation in the Skin I the Shock Syndrome J A M A. 123 891-893, 1943

[120] DiPalma J R Muss, I and Foster F I Reactive Hyperemia Ring Test in the Study of Pedal Lesions Caused by Arteriosclerosis Obliterans and Arterial Embolism Am Heart J 24 348-361 1942.

Chapter XV

DISEASES OF THE KIDNEYS

The relation of dermatoses to renal disorders fascinated the physicians of the nineteenth century more than the recent generations. Bright, in 1827 was convinced of the sympathy between the skin and the kidney and many famous authors have investigated this relationship more closely [illegible]

The kidneys being concerned with the excretion of water-soluble substances are functionally linked to the skin Under normal conditions the skin stores about 28 per cent of the body's water It takes up much more in edema[1144] which is the dominant symptom in acute diffuse glomerulonephritis and in some stages of other renal diseases. The loose texture of the skin and of the subcutaneous tissue affords more storage space than the muscles or even the serous cavities are able to provide. Along with water the skin stores chlorine and minerals. The vast vascular capacity of the skin provides an important regulating mechanism of the blood pressure which is the main power behind the urinary excretion The skin has an excretory function which however can only partially and occasionally replace renal excretion [114?]

Under normal conditions the skin as well as the kidneys excrete about 1300 c.c. of water daily but the kidneys are able to concentrate from the blood more than thirty times more urea and three times more NaCl than the tubules of the sweat glands. Thus even a damaged kidney usually excretes better than the skin and the skin alone is not able to replace the function of the kidneys.

Dermadromes were seen in approximately one-fifth of the series of 1100 patients with all forms of nephritis and nephrosis studied by Chargin and Keil.[illegible] These authors found that skin diseases occur more frequently in association with *azotemia* than in those without azotemia. In contrast to earlier observers [illegible] they found that *purpura* is the most frequent lesion associated with nephritis. All types of hemorrhagic lesions ranging from pinpoint petechiae to large extravasations were encountered. Chronic glomerular nephritis without edema seemed to predispose to hemorrhage far more than the other clinical types of nonsurgical kidney disease. Higher degrees of azotemia often cause intense purpura Sometimes the hemorrhagic tendency expresses itself only in a hemorrhagic component of a usually nonhemorrhagic dermatoses e.g. tinea *Pruritus* varying widely in intensity and in its sequelae may be the first symptom of nephritis (Otenlatory after Pringle[1 ?]) It occurred in 20 per cent of the cases of essential hypertension with azotemia and in 12 per cent of the instances of

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[illegible] Kreetz C Die klinischen Zusammenhänge zwischen Haut und Nierenerkrankungen, [illegible] 30 1933

[illegible] Ebner K Schweissdrüsen Verhandl d Gesellsch f. Verdauungs u Stoffwechselkr 13 213-[illegible], 1937

Pringle J J Skin Eruptions in Bright's Disease Practitioner 117 [illegible] 1901.

chronic glomerular nephritis with edema Its infrequency in all other groups of the series of Chargin and Keil[239] is striking Azotemia is probably the inciting factor Azotemia without pruritus occurs but if pruritus is present in uremia it is regarded as of serious prognostic importance [238] The pruritus may be explained by *dermatitic changes* which Rössle observed in almost all of 25 cases of



Fig 163 Purpura Chronic nephritis

uremia even when no gross changes were present [237] These inflammatory changes ranged from simple perivascular infiltration to necrotic and herpetiform pandermatitis The findings could not be confirmed entirely in an American series Here atrophy of the skin was the dominant pathologic feature Other pathologists have cautioned not to overrate the perivascular *infiltration* in the skin [240] which is often seen in glomerulonephritis

The *urea* content of the skin is usually high The appearance of crystalline urea as a thin white saltlike deposit on the skin especially about the nose the

[237] Rössle R Urämische Dermatitis Virchows Arch f path Anat 271 304-316 1929

[238] Rosenbaum S R Uremic Dermatitis Arch Dermat & Syph 23 974 1931

[240] Herxheimer G and Roscher W Hautveränderungen bei Nephritis, München med. Wchnschr 68 1451 191

neck and the shoulders[1 43] is known as *urea* (uremic) *frost*. It occurs most frequently in malignant sclerosis and essential hypertension (10 to 20 per cent after Chargin and Keil.[250]) A prolonged agonal period which allows the formation of the crystals together with a high urea content of the blood and of the skin seem to be the factors accounting for its relative frequency in these conditions.[250] The phenomenon of urea frost is more often seen post mortem than in life. It is still controversial whether the source of the urea frost is the sweat glands or the sebaceous glands. Its accumulation in the areas of accumulated sebaceous glands and its absence on the palms and soles seems to support the sebaceous gland theory while observations of crystals at the mouth of the sweat glands seem to prove the sweat gland origin. Urea frost is of ominous prognostic significance.

Erythematous bullous and urticarial eruptions in nephritis[[illegible]] have occasionally been described. Generalized exfoliative dermatitis is also mentioned in connection with the renal disease.[[illegible]] Some of these dermatoses may have been caused by septicemia. Ehrmann[[illegible]] saw in edematous patients aggregated vesicles about the head which rapidly formed oozing pink surfaces.

Fissural *eczema* is supposed to be more common in nephritis without edema. Grouped papular eruptions of great obstinacy were in the older literature known as erythema papulatum uremicum[[illegible]] (Merk after Ehrmann [[illegible]])

It may be mentioned in this connection that rabbits with experimental glomerular nephritis could be shown to be more sensitive to skin irritation from tar than the normal controls.[[illegible]]

A progressive febrile dermatosis probably of bacterial origin occurring relatively often in *lipid nephrosis* is referred to as *erysipeloid*. (This condition should not be confused with the erysipeloid of Rosenbach.) The eruption is seen on the abdomen and thighs spreading from there with an erythematous circinate flush and tender border. There may be recurrent attacks[[illegible]] with occasional abscess formation.[[illegible]]

The complexion of patients suffering from *contracted kidney* is often yellowish. This discoloration is restricted to parts exposed to light. The pigmentation is explained[[illegible]] by the retention of urochromogens which under the influence of light change into their color just as they do in a pale urine from an arteriosclerotic kidney. There is no retention of urochromogens in acute nephritis.

[[illegible]] Sachs, O. Erythema exsudativum multiforme und Erkrankungen innerer Organe, Arch. f. Dermat. Syph. [illegible] 35-72, 1909.

[[illegible]] Duckworth, D. A Case of Chronic Interstitial Nephritis in Which Dermatitis Exfoliativa Supervened. Brit. J. Derma. [illegible] 1900.

[[illegible]] Ehrmann, S. Beziehungen der ekzeme [illegible] Erkrankungen zu inneren Leiden. Halle 1924, Carl Marhold.

[[illegible]] Kristanof, [illegible] A. La réactivité de la peau et la fonction des reins, Ann. de dermat. et syph. 7 [illegible]-70, 1936.

[[illegible]] Aldrich, C. A. and Boyle, H. H. Erysipelas-Like Lesions of Skin in Nephrosis, Am. J. Dis. Child. [illegible] 1923.

[[illegible]] Schwarz, H. and Kohn, J. L. Bacteremia and Skin Manifestations in Lipoid Nephrosis, Am. J. Dis. Child. [illegible] 763-774, 1929.

[[illegible]] Becher, E. Untersuchungen über das Zustandekommen der gelblichen Hautfärbung bei Niereninsuffizienz. München. med. Wchnschr. 77: 1922, 1930.

Carotinemia is always present in nephroses but only in 10 per cent does the skin become noticeably yellow[1187]

In *acute nephritis* the *capillaroscope* may reveal narrow arterial and wide tortuous venous segments The subpapillary venous plexus is well visible and the circulation is slowed These changes may precede the outbreak of nephritis[1174] (Goth after Niekau[1188]) suggesting the primarity of the capillary damage

Herpes zoster has often been seen in attacks of *nephrolithiasis*[1136] Severin[1138] found that these eruptions corresponded to the eleventh and twelfth dorsal and the first and second lumbar segments Their area was found identical with the associated Head s zones. Some cases of *pruritus* and *obstinate eczema* in chronic nephrolithiasis were relieved by operation They can be interpreted as caused by the infected focus and by parenchymal damage caused by calculi and in fection

Pruritus is a common symptom in all types of chronic urinary *retention* Thus it is frequently and early observed in benign hypertrophy of the *prostate* and occurs also in stricture of the urethra It is good advice to examine prostate and bladder in all unexplained cases of pruritus and secondary pyoderma present in elderly men.[12,1134] In rare instances pruritus vulvae may be caused by neph roptosis.[1189]

Though not being the cause of dermatoses *Peyronie s disease* or induration of the tunica albuginea of the corpora cavernosa penis is possibly a manifestation of a systemic disorder which may also cause surface symptoms Touraine and Ruel [1190] call hereditary polyfibromatosis the tendency to form nodular nonencapsulated indurations in many parts of the connective tissue While the associa tion of induration of the corpora cavernosa with Dupuytren s contraction of the palmar aponeuroses has long been recognized keloids fibromas of the fingers and similar connective tissue lesions are also seen together with Peyronie s disease Simple dominant heredity is supposed to exist. Similar hypotheses of earlier authors have not found acceptance.[1191]

[1187] Boeck, W C and Yater W M Xanthemia and Xanthosis (Carotinemia) J Lab. & Clin. Med 14 1129-1143 1929.

[1188] Lutz, W Stoffwechsel und H ut, Handb. d H Ok 3 1929

[1189] Strickler A Ptosis of Kidney as Cause of Pruritus Vul ae, Arch. Dermat. & Syph 90 405 1914

[1190] Touraine, A and Ruel, H Hereditary Polyfibromatosis, A de Dermat et syph. 5 1-5, 1915

[1191] Vaderland W Dupuytren sche Kontrakt ad Beruf Arch f Gewerbepath Gewerbehyg 3 33-41 1932

Chapter XVI

DISORDERS OF THE ENDOCRINE GLANDS

THE PITUITARY BODY

The hormones of the *anterior lobe* of the pituitary stimulate the activity of the thyroid the parathyroids the mammary glands the islands of Langerhans in the pancreas the adrenal cortex the gonads and the placenta The carbohydrate and fat metabolism and the growth are influenced either directly or indirectly by the effects on the above-named glands.[illegible]

The *intermediate lobe* activates the melanophores in the skin of amphibia Its physiology in man is little understood.

The *posterior lobe* secretes two principles which act on the smooth muscle fibers It profoundly influences diuresis by the production of an antidiuretic hormone

Frohlich s Syndrome

Dystrophia adiposogenitalis or Fröhlich s Syndrome is the triad of obesity particularly of the lower trunk genital underdevelopment and pituitary symptoms. The latter seem due to hypoactivity of the anterior lobe and the pars intermedia. Fröhlich s Syndrome is one of the commonest endocrine diseases especially of young males. This was demonstrated in the induction centers during the last war [illegible]

Dermadromes.—In the younger patients the skin is smooth and pale and the veins are well visualized Cushing remarks that persistent freckles on exposed areas is a characteristic of most cases of hypopituitarism Perspiration is scant or lacking [illegible] The subcutaneous fat which is particularly abundant on the hips sometimes seems to suggest a deep seated nonpitting edema Striae are seldom seen The pubic and axillary hair is absent and the lateral third of the eye brow is often missing Ordinarily the scalp hair is not only unaffected but seems to be especially well developed If the under-developed gonads start functioning e g after successful treatment w th anterior pituitary hormone the body hair and the other secondary sex characteristics may still develop Several authors emphasize the small thin under-developed nails which do not show lunulae at their bases. Onychogryphosis fragility of the nails and opaqueness of the nail substance ha e occasionally been noticed.

[illegible] Sevringhaus, E. L. Endocrine Therapy in General Practice Chicago Ill 1940, Year Book Publishers Inc

[illegible] Ryerson E. H Hormones of the A erior Lobe of he Pituitary Body J A M A 125 [illegible], 1944

[illegible] Rowntree Endocrine Diseases as Revealed by 13,000,000 Examinations of Registrants, J Clin Endocrinol 4 [illegible] 1944

[illegible] Cushing, H The Pituitary Body nd Its Disorders, Philadelphia, 1912

In the rare *Laurence Moon Biedl* syndrome which consists of dystrophia adiposogenitalis retinitis pigmentosa mental deficiency and polydactylism cutaneous peculiarities other than in Fröhlich s syndrome have not been recorded

L. Fränkel noticed the failure of the lateral parts of the escutcheon to develop in patients with *pituitary infantilism* (After Mussio Fournier [11])



Fig 164 Fröhlich type Male aged 18 years. Obesity gynecomastia, lack of pubic hair

The complete absence of secondary sex characteristics, dryness of the skin freckles and hypotrichosis of body and scalp is the rule in *dwarfs of pituitary origin* (Type Lorain Levi) The scalp loses some or much of its hair mostly in the vertex area less so at the margins. This vertex type of alopecia has been observed in several pituitary conditions (Engelbach) *Cutis laxa* and *Ehlers Danlos syndrome* has in some cases been related to hypopituitarism [1]

Cachexia Pituitaria Simmond s Disease

Simmonds Disease occurs almost exclusively in women after childbirth The cause is atrophy or destruction of the glandular part of the pituitary

The early stages of this syndrome resemble myxedema Later with increasing wasting amenorrhea or in the male impotence develops Muscular weakness extreme loss of fat hypotension apathy and hypersomnia low temperature low blood sugar low basal metabolism and eosinophilia compose a picture which can easily be confused with other cachectic conditions. Good and sometimes dramatic results have been obtained with anterior lobe extracts.

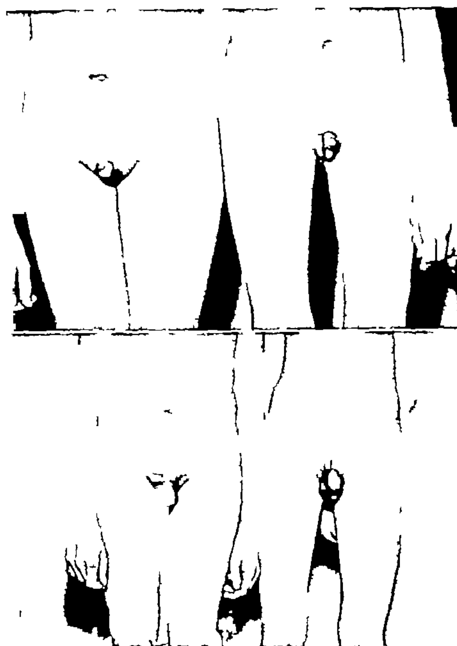


Fig. 43.—Brothers, aged 21 and 27 years. Arrested sexual development [illegible] the age of 14. Froehlich type. Almost no pubic hair; obesity. *Below*, after one year of treatment with gonadotropic hormone and testosterone. (Courtesy Wisconsin General Hospital.)



Fig 166 —Laurence-Moon-Biedl syndrome Not polydactylism (Courtesy Wisconsin General Hospital)

Dermadromes.—The skin is waxy pale or yellowish and slightly edematous Later the turgidity disappears and the skin becomes dry wrinkled and slightly scaly or in some areas especially about the hands and feet glossy chilblain like or even sclerodermatic. There is a definite tendency toward pigmentation The pubic and axillary hair as well as the eyebrows and beard disappear completely in the fully developed syndrome[166-171] In some instances not a single lanugo hair can be detected on the whole body surface The eyelashes and the scalp hair usually stay The nails and teeth fall out or suffer dystrophic changes.[71]

Acromegaly

Acromegaly is caused by hyperactivity of the eosinophile cells of the anterior pituitary which are responsible for the growth stimulating hormone Eosinophile (acidophile) tumors and eosinophile hyperplasia have often been found

The overgrowth affects the skeleton and other systems Maxillary rather than mandibular prognathism is characteristic of the true acromegalic The nasolabial folds deepen and the ears seem to be set back The teeth become separated and the hands and feet enlarged The viscera take part in the unnatural growth The hyperfunction of the anterior pituitary may be followed by hypo-

[166] Berblinger W Zur K[illegible] der Simmondsschen Krankheit Endokrinologie 18 209 1931

[167] Die Simmondssche Krankheit Umfrage Med Klin 32 59 [illegible] 13 7 1936

[168] Zoltschan J Dermatologische Bezieh ngen der Simmondsschen Leiden Hungary [illegible] 13 177 179 193 Zbl 84 233

[169] Cost [illegible] F [illegible] clinic alla conoscenza della mala ia di Simmonds (cachessia ipofisaria Policlinico sez med 38 31 264 [illegible]

[170] Herman K Zur Klinik der Simmondsschen Krankheit München med Wchnschr 77 1020, 1930

[171] Graubner W Die hypophysäre Kachexie Simmondssche Krankheit Ztschr f klin. Med 101 249 1925

function and incomplete regression of the acromegalic signs in the soft tissues.[166] Such a regression in the skeletal system is hardly possible. Therefore the typical cutaneous signs of acromegaly may be absent in fully developed skeletal acromegaly.

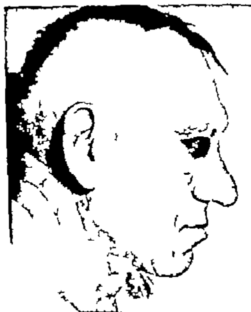


Fig. 167.—Acromegaly. Note freckles, small fibroma, deepening of furrows, especially nasolabial [illegible] folds. Ear seems to be set back. (Courtesy Wisconsin General Hospital.)

Dermadromes.—In acromegaly the skin, like the bones and the viscera, is overdeveloped in every direction and can be compared to a normal skin under a magnifying glass. The surface is coarse, the furrows deepened, and the connective tissue thickened or somewhat edematous. Moles may appear or existing ones grow. Combination with Recklinghausen's disease has been observed a number of times.[73] The cutaneous glands are enlarged and their hyperactivity is indicated by moisture and seborrhea. Comedos and follicular keratoses are marked. Acne is not unusually common. The pigmentation is moderately accentuated.[166, 73] The hair growth is increased in about one-fourth of the cases, occurring[168] especially on the body, so that in women a more masculine habitus results. In only seven per cent does the hair growth decrease.[73] By feeding young rats or injecting young dogs with anterior lobe extract the hair has been shown to become thicker than in the controls.[98] (Robertson 1917 after Musso

[166] Atkinson, F. R. B.: Acromegaly. From a Study of [illegible] 1931. Endokrinologie 17: [illegible]

[167] Atkinson, F. R. B.: Acromegaly. London [illegible] John Bale Sons & Danielsson, Ltd.

[168] [illegible] and [illegible]: [illegible] of the Endocrine Glands. II. The Pituitary. Endocrinology 12: [illegible]

[169] [illegible] L. M.: Acromegaly [illegible] Endocrinology 1: 401 1938.

[98] [illegible] E.: Influence of Pituitary Feeding Upon Growth and Sexual Development. Bull. Johns Hopkins Hosp. 27: [illegible]

Fournier[14]) Occasionally blond hair becomes darker and straight hair becomes curly and negroid [1177] The scalp hair may become thin on the vertex [1178] and premature greying may be seen The nails participate in the general hypertrophy becoming broad striated sometimes spoon-shaped (coilonychia)[13]



Fig. 168 Fig 169

Fig 168 Cushing syndrome Broad purplish striae obesity (Courtesy Wisconsin General Hospital.)

Fig 169 Broad purplish striae in Cushing' syndrome (Courtesy Wisconsin General Hospital.)

and occasionally long (Walker after Atkinson[1179]) Varicose veins are not uncommon

Cutis verticis gyrata [79] is a congenital anomaly consisting of an excess of scalp which causes the skin of the vertex to form folds and furrows resembling

[1177] Aschner B Der Einfluss der Hypophyse auf die weiblichen Geschlechtsorgane Med Kli 20 1 1 1653 1924

[1178] Engelbach, W Hair Growth and Pigmentation, M Clin North America, 9 1-41 1925

[1179] Jadassohn J Eine eigentümliche Furchung Erweiterung Verdickung d Haut am Hinterkopfe 9th kongr Deutsch derma Ges Bern, 1906.

the gyri of the brain This peculiar and rare lesion has been observed more than nine times in acromegaly which is often enough for it to be considered an occasional pituitary dermadrome [1130-1134]

The combination of acromegaly and xanthoma diabeticorum has been reported five times in three years.[1135] Persistent edema of the eyelids face and extremities is well known and transitory circumscribed edema of the Quincke type has also been reported.[1136]

Basophile Adenoma

Basophile Adenomas produce a characteristic group of symptoms now well known as Cushing's syndrome The neoplasm develops mostly in young adults The highest age in twelve cases recorded by Cushing was 25 years. The patients are definitely undersized since they become shorter during the disease The duration of the ailment averages slightly over five years Adiposity is characteristically confined to the face neck and trunk the extremeties being spared. The fat deposits are often tender and develop quite rapidly The round face

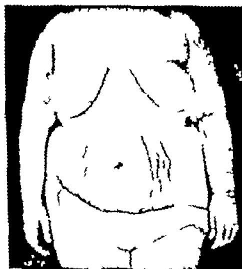


FIG 70 Cushing syndrome Female aged [illegible] years Amenorrhea since age of 13 [illegible] striae [illegible] blood cholesterol 200 Normal eye grounds (Courtesy the late Dr [illegible])

[1130] [illegible] F Fall von Diabetes mellitus und Akromegalie mit Cutis verticis gyrata, [illegible] 1220-1223 [illegible] 63 527

[1131] [illegible] Farmer H M and Wieder L M Cutis Verticis Gyrata With Associated Pituitary Disease Arch Dermat & Syph [illegible]

[1132] [illegible] Sur la morphogenèse de la pachydermie occipitale verticillée ("Cutis verticis gyrata") [illegible] des rapports avec acromégalie Bull. Soc. franç. de dermat. et syph [illegible] 1922

[1133] [illegible] A Hypophysenbestrahlung bei Cutis verticis gyrata, Acta radiol [illegible] 1924.

[1134] Weber F [illegible] verticis gyrata Proc Roy Soc Med [illegible] 1922

[1135] [illegible] Alopecia universalis und Nervensystem Akromegalie und Erkrankung, Deutsche Ztschr f Nervenh [illegible]

is often described as a full moon face but the facial expression is more painful than jolly Weakness kyphosis back aches amenorrhea in the female and impotence in the male are other symptoms

Dermadromes.—The most striking dermadrome is the development of broad purplish striae atrophicae mainly in the lower and lateral parts of the abdominal skin They were present in all of Cushing's twelve cases and have since been seen in a great number of instances.[1] It seems as if the basophile adenoma produces a toxic substance with a special affinity to the elastic fibers Their resistance and elasticity appear to be weakened so that they tear on relatively slight strain (see striae of pregnancy)



Fig 171 —Cushing syndrome Livedo reticularis (Courtesy Wisconsin General Hospital)

The skin is often hyperpigmented[1] It is dusky or copper colored especially the face It is usually dry Purpura traumatica has frequently been observed

Hypertrichosis of the face and trunk has been constantly found in females and preadolescent males

Many secondary endocrine disturbances are on record such as those due to dysfunction of the thyroid and adrenals. Diabetes has been recorded

The resistance against infections is lowered this leads to frequent pyodermas Infections are often the immediate cause of death

[1] Jonas Cushing Syndrome Med Klin 1936 1 614

Chapter XVII

DISORDERS OF THE ENDOCRINE GLANDS

THE THYROID GLAND

Thyroxin the hormone of the thyroid gland stimulates the oxidative processes of the body

The influence of the thyroid on the skin is manifold.[1107] The removal of the gland in animals increases the content of water and chlorides the total nitrogen and the protein derivatives in the skin Administration of thyroxin decreases the cutaneous chlorides and the water and increases the sugar and nitrogen Some of these effects may be reversed with high doses of thyroxin Thyroidectomy increases the capacity of the skin to swell in 1/10 normal HCl (Quellung) Thyroxin causes higher and more prolonged skin and blood sugar tolerance curves. The resorption time of a saline wheal is prolonged after thyroidectomy and shortened under the influence of thyroxin while the resorption of potassium iodide shows an opposite tendency Thyroxin increases the sensitivity of the skin to X-ray and ultraviolet rays.[1108]

Hyperthyroidism (Graves Disease Basedow s Disease Thyrotoxicosis Exophthalmic Goiter)

The skin in hyperthyroidism is smooth thin and elastic with a velvety feel[1109] This is in part a constitutional characteristic and is often present before any symptoms of the disease become apparent. The skin is moist warm and rosy but the color is unstable The elevation of the temperature is roughly proportional to the increase in the metabolic rate The difference in temperature between covered and exposed skin areas is less pronounced than in a person with a normal metabolism It seems that the thinness of the skin as well as the increased temperature and moisture helps to free the body from a surplus of heat created by the elevated metabolism. The patients usually complain of excessive warmth and like to sleep with the limbs uncovered

Dermadromes.—Erythema of the chest and back and of the parts where the clothing presses is common [1110] Unexpectedly the capillary microscope shows that the capillaries are thinner than normal[1111] although observations of enlarged

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[1107] Bohnsted R M. Experimentelle Untersuchungen über die Beziehungen zwischen Haut und innersekretorischem System, Arch f exper Path 170 474, 1932-1933.

[1108] Ellinger F Ueber die Bedeutung der Schilddrüse für den Ablauf der Strahlenreaktionen an der Haut, Klin Wchnschr 11 1049 1932

[1109] Tousman, J H Changes in the Skin in Thyrotoxicosis, Am J M Sc 181 681-682, 1931

[1110] Means, J H The Thyroid, Springfield, Ill 1937, Charles C Thomas.

[1111] Michael, M and Buschke W Ueber das Verhalten der Hautcapillaren beim Morbus Basedowii, Klin. Wchnschr 11 1842 1843 1932

capillaries have also been made.[illegible] Dilatation of the arterioles of the subpapillary plexus accounts for the increased rate of the peripheral blood flow and the high skin temperature (Bansi after Michael and Buschke[illegible]) Due to the increased moisture the electric resistance of the skin is low

Hyperhidrosis is often as marked and as weakening as in pulmonary tuberculosis [illegible] Seborrhea, acne and comedos indicate overactivity of the sebaceous glands. In about 50 per cent of the cases[illegible] there exists a tendency to increased *pigmentation* The hyperpigmentation is often inconspicuous this explains the much smaller percentages in some series. Youmans[illegible] sees a difference from the pigmentation in Addison s disease mainly in its lesser degree and in the lack of pigmentation of the mucous membranes. The pigmentation seems to have the older authors more impressed than those of recent years. [illegible] The hyperpigmentation of the eyelids is often regarded as suggestive of hyperthyroidism (Jellinek s sign)

Vitiligo has been seen in roughly 10 per cent of the cases.[illegible] This is high enough to warrant a basal metabolism test in all cases of vitiligo

There exists a marked tendency to transient *edema* Unexplained puffiness of the eyelids[illegible] and ankles chronic *urticaria*[illegible] and angioneurotic edema should cause the physician to think of hyperthyroidism The resorption time of intradermally injected saline (McClure-Aldrich test) has been found to be prolonged in untreated cases with a return to normal after operation or iodine treatment [illegible] The validity of these findings however has been disputed [illegible]

Marañon s sign is the more marked and longer lasting red dermographism in the skin covering the thyroid gland as compared with the red dermagraphism in other areas. The sign is frequently positive in hyperthyroidism but is not specific.[illegible]

The *hair* is very sensitive to the toxic effects of hyperthyroidism Sainton[illegible] and his collaborators noticed diffuse or circumscribed loss of the hair in 43 per cent of their 180 cases. The vertex and the temples are especially affected [illegible]

[illegible] Roberts, E. and Griffith, J Q J Quantitative Study of Cutaneous Capillaries i Hyperthyroidism, Am Heart J 14 [illegible]-603 1937

[illegible] Michael, M and Buschke W Das Verhalten der Hautcapillaren beim Morbus Basedowii, Deutsche med Wchnschr 59 134-136 1933

[illegible] Hyde and M Ewen The Dermatoses in Exophthalmic Goitre Am. J M Sc 125 1000 1903.

[illegible] Bram ell B Anemia and Diseases of he Blood-forming Organs and Ductless Glands, 1899

[illegible] Habermann, R Paratypische Pigmentanomalien, Handb d H Gk 4 2 796-834 1933

[illegible] Dore Cutaneous Affections Occurring in the Course of Gra es Disease Brit J Dermat 12: 353 1900

[illegible] Bo[illegible] J N Chronic Urticaria, Thyro-Adrenal Syndrome, How t Determine the Direction of the Dysfunction, and What Type of Agents t Employ in I Treatment, Sou h. M J 22: 669-672 1929

[illegible] Mora, J M I racutaneous Salt Solution Test in Thyrotoxicosis, Am J M Sc. 177 210 1929

[illegible] Efroesi-Ryss, R Le signe de Marañon et sa signification dans le goitre exophtalmique Thèse de Paris 1928

[illegible] Sainton, P and Simonnet, H Les troubles d la fonction thyroidienne et leur action sur le système pileux A de méd 29 263-270 1931

[illegible] Sainton, P and Maman H Hyperthyroidisme provoqué par la thyroxine synthétique chez un malade atteint d un syndrome pluriglandulaire vec sclérodermie et cataract Bull et mém Soc méd d hôp de Paris 43 1643 1927

[illegible] Foerster O H The Relation of Internal Secretions t Cutaneous Disease J Cutan. Dis 34 1 1916

Typical *alopecia areata* is not infrequently associated with hyperthyroidism an observation already made by Basedow [1294-1295] Alopecia as well as canities may affect the head hair the beard the eye lashes the eyebrows and the body hair Some authors emphasize the frequency of alopecia of the lateral third of the eyebrows. White spots in the hair have often been recorded [1296] Improvement of the hyperthyroid condition may be followed by improvement of the alopecia. Universal baldness as well as hypertrichosis are rare [1297]

Alopecia as well as canities has been experimentally produced in animals by feeding with human or animal thyroid or with thyroxin [1298 1299]

Melanization however has also been observed after thyroid feeding [1300 1301] Chickens are much better fit for these experiments than cats and rabbits.[1302] The sudden production of alopecia and canities after mental shock and terrifying experiences, which so far has not been well substantiated could be explained by sympathetic stimulation of the thyroid [1303-1305]

In thyroidectomized rabbits regeneration of plucked hair is delayed or absent.[1306-1307] Thyroid extract feeding speeds the regeneration of plucked feathers in pigeons.[1308]

There is no relation between the severity of the hair changes and the severity of the hyperthyroidism This refers to the clinical observations as well as to the animal experiments. The blood of thyroidectomized horses compensates the effect of thyroid feeding on the integuments.[1299] The extract of toxic goiter is reported to be more effective on the plumage of chickens than the extract of simple goiter [1309]

In spite of these and other suggestive experiments the etiology of *alopecia areata* has not been elucidated It seems that many factors are able to produce

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[1294] Von Basedow G A Exophtalmus durch Hypertrophie des Zellgewebes in der Augenhöhle Wchnschr f d ges Heilk., Berlin, 1840

[1295] Sabouraud R Diagnostic et traitement des affections du cuir chevelu, Paris, 1932, Masson et Cie

[1296] Peyret, J Dystrophies et dyschromies des formations épidermiques au cours du syndrome d Basedow (M lanodermie exceptée) Thèse de Paris, 1926.

[1297] Schereschewsky N A De l'influence des sécrétions endocriniennes sur la pousse des poils, Rev franç d Endocrinol 3 301-312, 1925.

[1298] Zavadovski Effect of Single Doses of Thyroid Gland on Fowls, Endocrinology 9: 125-136, 232-241 1925

[1299] Zavadovski, B M Hormone und das Gefieder der Vögel. Endokrinologie 10 23-36, 1932.

[1300] Cole and Reid Melanization After Thyroid Feeding, J Agricult Research 29: 1924

[1301] Crew and Huxley Melanization of Chicken Feathers After Thyroid Feeding, Vet. J. 79 1923

[1302] Sainton, P Maximin M and Mamou, H L hyperthyroïdisme et son action sur les phanères, Bull Soc franç de dermat et syph. 35 23 27 1928

[1303] Lévy Franckel, A and Juster E Recherche sur le mécanisme physiopathologique de la pelade II Pelades traumatiques et pelades par choc émotif Ann. de dermat et syph 2: 1074-1088, 1921.

[illegible] Rasmi Posttraumatische Alopecia areata Ibid 44 453, 1933

[1305] Barber H W Post Traumatic Alopecia Areata, Proc Roy Soc Med 25 923-926, 1932

[1306] Furuya K Beiträge zur Physiologie der Drüsen. Wachstum der Haare und Schilddrüse Biochem Ztschr 147 423, 1924

[1307] Cooper Z K Endocrine Glands and Hair Review of Literature Arch Dermat. & Syph 21 1007 1029 1930

[1308] Larionov W Th Woitkewitsch, A A and Brisky N W Die Regeneration des Gefieders der Tauben bei verschiedenen hormonalen Einwirkungen, Endokrinologie 12 [illegible]-422 1933

[1309] Sainton, P H Simonnet, and Barbé P Action comparée des extraits de glande thyroïde de basedowiens et de goitreux sur le plumage des gallinacées, Bull Soc franç de dermat et syph. 37 484-486, 1930

the same typical picture which is more than twice as common in men as in women.[illegible] Infection [illegible] seems plausible in a number of cases. Hyperthyroidism as well as hypothyroidism[illegible] has been seen too often in alopecia areata to be dismissed as a coincidental occurrence.[illegible]

Fig. 172.

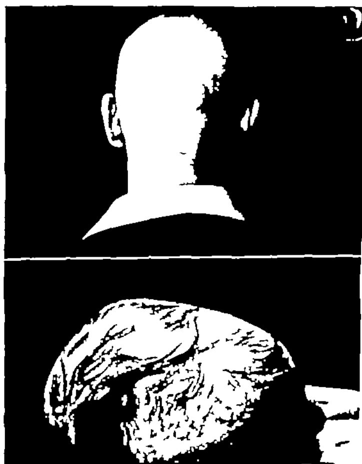


Fig. 173.

Fig. 172.—Alopecia totalis. Moderate hypothyroidism.
Fig. 173.—Same patient after treatment with thyroid.

[illegible] Waisman, M., and Kepler, E. J.: Alopecia Areata: An Appraisal of Endocrine Factors in Its Causation, J.A.M.A. 116: 2004-2006, 1941.

[illegible] Cederberg, A.: Untersuchungen über die Alopecia areata mit besonderer Berücksichtigung ihrer Aetiologie. Zugleich ein Beitrag zur Vitiligofrage, Duodecim 47: 835-853, 1931; Zbl. 40: 339.

[illegible] Spitzer, R.: Zur Aetiologie und Symptomatologie der Alopecia areata, Arch. f. Dermat. u. Syph. [illegible] 1939.

[illegible] Throne, J.: Basal Metabolism in Dermatological Conditions, New York State J. Med. 30: 259-264, 1930.

[illegible] Ribera, V.: Zur Pathogenese der Alopecia areata, Česká dermat. 13: 53-75, 96-102, 107-129, 135-141, 1932; Zbl. 43: 433.

[illegible] Bolajakovic: Alopecia areata und Sororiasis, Zbl. 39: 142, 1931-1932.

[illegible] Merenlender: Alopecia areata mit bedeutenden Pigmentstörungen, Zbl. 41: 343, 1932-1933.

Wasman and Kepler [illegible] found a metabolic rate of less than minus 10 per cent in 25 per cent of their cases

The occasionally striking success of thyroid medication supports to some extent the thyroid etiology of some cases, though the general stimulating effect of thyroid preparations has to be taken into account. A pituitary etiology has been claimed on the grounds of (1) supposed roentgenological changes in the sella turcica[illegible] which was not confirmed by Wasman and Kepler [illegible] (2) coincidence with pituitary symptoms and (3) successful treatment with anterior lobe extracts[illegible] and radiation of the pituitary [illegible] There are some cases with ovarian testicular and adrenal findings in alopecia areata with corresponding hormone therapeutic results There are other arguments in favor of a pituitary etiology Vitiligo or chloasma was present in about 10 per cent of Wasman and Kepler's[illegible] series. The influence of mental strain and shock is important. Preceding infections have also been accused

The *nails* have occasionally been found altered in hyperthyroidism. Longitudinal and transverse grooves, atrophy onycholysis and leukonychia have been described

Hypothyroidism

However different the symptomatology of congenital and acquired thyroid deficiency may appear there is little difference in the dermadromes of both types. The dermadromes of hypothyroidism appear early and therefore they deserve particular attention.[illegible] It is necessary to emphasize that the fully developed syndrom is rare while cases having some of the symptoms occur quite frequently Severe deficiencies of the thyroid have been observed with or without skin changes.

In hypothyroidism the skin is pale and often slightly yellowish due to carotenemia.[illegible] It seems that the liver is unable to form Vitamin A from carotene due to the lowered metabolism The skin is cool to the touch and the patient feels the cold more intensely than normal persons. The coolness of the skin is considered to be one of the earliest symptoms in the whole syndrome of hypothyroidism The lowered temperature is especially noticeable in the ex

[illegible] Eller Alopecia Totalis and Folliculitis, Arch Dermat & Syph 20 403, 1929

[illegible] Tsukada, Ueber auffallenden Heilerfolg des Hypophysenvorderlappenhormons gegen Alopecia, Jap J Dermat pp [illegible] 1933 Zbl 48 [illegible], 1933.

[illegible] Bengtson B N Anterior Pituitary Therapy in Alopecia Totalis, Clin Med & Surg. 40: [illegible] 1933

[illegible] Tsukada, and Akaishi K Weitere Erfahrungen aus der Hormontherapie der Alopecia areata, nebst klimatologischer biochemischer und neurologischer Untersuchung, Jap J Derm & Urol. 34 1933

[illegible] White A W Pituitary Extract in the Treatment of Alopecia, Canad M A J 31 301 1934

[illegible] Urbach E Erfolgreiche klinische Therapie bei endokrin bedingtem Haarausfall, Zbl 33 310 1930

[illegible] Fedenko A Chronic Insufficiency of the Thyroid Gland Russk Vest Dermat 5 Nrs 4-10 1927 Zbl 23 160

[illegible] Kress-Apajalahti L Wirkung der Thyroidinbehandlung auf die Haut des Myxödemkindes Histologische Untersuchungen, Acta Soc med Duodecim. 18 2 1 13, 193[illegible] Zbl 40 630, 1932.

[illegible] Escamilla R F Carotinemia in Myxedema Explanation of Slightly Icteric Tint, J Clin. Endocrinol 2: 33-41, 1942

[illegible] Mandelbaum, T Candel, S and Millman, S. Hypothyroidism, Hyperlipemia and Carotenemia, J Clin Endocrinol 2: 465-467 1942

tremities where it is sometimes combined with acrocyanosis and associated complications like chilblains and tuberculids.[1337] Several authors[1338-1339] saw deep ulcerations of the legs connected with hypothyroidism and they advised treatment with thyroid by mouth and thyroid powder or thyroid salve locally. The skin is dry especially on the extensor surfaces of the extremities. In some cases of acquired myxedema marked keratosis palmaris and plantaris was observed and successfully treated with daily doses of 0.2 — 0.3 Gm. of thyroid.[15,1338,1340,1341] The basal metabolism has often been studied in congenital ichthyosis. The findings and the results of thyroid therapy are controversial.[1342-1344]

The dryness of the palms and arm pits (anhidrosis) is striking since the secretion of the sweat glands and of the sebaceous glands is reduced or completely absent. Nevi and moles may appear and desquamation is pronounced due to the dryness and to the tendency toward increased keratosis. In advanced or neglected cases this may cause a picture similar to ichthyosis particularly around the knees and elbows and also in the axillary and inguinal folds (Reuter in discussion to Cornbleet and Cohen[1345]). In some cases of congenital ichthyosis thyroid therapy seems to have given relief.[1346-1348] Itching is a frequent complaint.

The edema in fully developed myxedema is nonpitting and firm. It is most marked in the face and in the ears which sometimes have a cauliflower like appearance.[1349] The facial features are coarse. The term "eskimo face"[349] is significant. Eyes and nose appear smaller than normal, the latter especially in children is saddle shaped. This sign is commonly met with. The eyelids, especially the lower lids, the skin of the forehead, the ears and the lips are swollen and cause a deepening of the nasolabial and forehead folds. The supraclavicular fossae and the dorsa of the hands and feet are other sites of increased myxedematous or fat pads. The swelling may extend to the mucosae. The tongue, the uvula and the nasal and laryngeal mucosae may become involved with a consequent disturbance of the voice. The thick protruding tongue of the cretin is a familiar picture.

[1337] Covisa and Bejarano: Tuberculide and Hypothyreoidismus, Actas dermo-sif. 23: 45, 1931; Zbl. 3: 359.

[1338] Cohen, M. H.: Leg Ulcers Due to Thyroid Dysfunction, J. A. M. A. 103: 283-285, 1934.

[1339] Eppinger, H.: Torpide Hautgeschwüre als Symptome eines lokalen Myxödems, Klin. Wchnschr. 10: 442-443, 1931.

[1340] Massia Fournier, J. C.: Kératodermie plantaire et palmaire chez une hypothyroïdienne. Sa guérison par la thyroïdine, Bull. et mém. Soc. méd. d. Hôp. d. Paris, 48: 1236-1237, 1932.

[1341] Cervino, J. M., Vertolini, A. and Larrosa Helguera, R. A.: Keratodermias of Hands and Feet and Thyroid Deficiency, Endocrinology 23: 614, 1938.

[1342] Krogh, M. and With, G. O.: The Standard Metabolism in Ichthyosis, Acta dermat.-venereol. 3: 444, 1922; Zbl. 91: 403.

[1343] Siemens, H. W.: Untersuchungen über d. Stoffwechsel Ichthyotischer, Arch. f. Dermat. & Syph. 149: 466-478, 1925.

[1344] Porter, A.: Basal Metabolism in Ichthyosis, Brit. J. Dermat. 38: 478-491, 1926.

[1345] Cornbleet, Th. and Cohen, D.: Pellagra and Myxedema, Arch. Dermat. & Syph. 42: 1140, 1940.

[1346] Sieben, H.: Ichthyosis als Folge endokriner Störung, Derma. Wchnschr. 94: 710-712, 1932.

[1347] Desaux, G. and Neuhaus, C.: Myxödem und Ichtyosis, München. med. Wchnschr. 76: 1664, 1929.

Idenouse, S.: Ichthyosis simplex, J. p. J. Dermat. & Urol. 34: 107, 1934.

[1349] Petracek, E.: Ein Fall von chronischer Insuffizienz der Thyreoidea. Ein Beitrag zur Pathologie des Ödems, Česká dermat. 12: 233-241, 1931; Zbl. 39: 72.

Increased pigmentation especially on the forehead around the lids and some distance from the mouth occurs. Severe bronze-colored pigmentation of the body has been observed in cachexia thyreopriva.[illegible] However it is doubtful whether or not the pigmentary changes are caused by the hypothyroidism Curschmann[illegible] infrequently found grey hair in adult patients. He relates this finding to his observation that adult patients with chronic myxedema due to their lowered metabolism, age later than normal persons. This author found patients with compensated myxedema at the age of sixty and seventy years look like forty five. Other authors frequently found premature greyness in myxedema

Loss of hair is common in hypothyroidism This clinical observation is supported by observations on thyroidectomized animals The hair in myxedematous patients is dull dry brittle and easily wears off and sheds. The axillary and pubic hair becomes scanty or absent.[15] The margins of the scalp tend to become bald Bald spots not always of the common areata type occur and may respond well to thyroid therapy although this treatment is ineffective in the majority of the cases of alopecia areata. In women baldness of the forehead is sometimes striking

The significance of the loss of hair of the lateral third of the eyebrows as a symptom of hypothyroidism especially in children (Hertoghe s or Levy and Rothschild s sign) is not generally recognized It is less pronounced in the Teutonic races with whom thinner eyebrows are considered normal

In some cases of hypothyroid infantilism the lanugo hair persists in considerable strength but disappears with thyroid medication [15]

The *nails* are often changed. Dystrophies have been found in some series up to 93 per cent.[illegible] The size can be decreased the normal curvature absent and the nail may be very thin Decrease in size brittleness, longitudinal and transverse grooving defective lunulae and white spots in the matrix are common [illegible] The rate of growth is markedly reduced [illegible]

The resistance to pyogenic infections blepharitis and erysipelas is low in myxedematous patients. The clinical appearance of the myxedematous skin is the result of edema and excess mucin in the epidermis degeneration of the collagen and elastic fibers and a sparse cellular infiltration about the vessels.[illegible] The electric resistance of the myxedematous skin is increased [illegible]

Circumscribed Myxedema

This not extremely rare condition is a paradoxical one (Trotter in disc to Freudenthal[illegible]) It consists of pretibial circumscribed lesions which are

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[illegible] Korber A Die Pathologie der Schilddrüse XXIII Congr inn Med Wiesbaden, pp 50-127 1906

[illegible] Curschmann, H. Zur Klinik und Pathophysiologie des Myxoedems (insbesondere der gu ar tigen inkompletten Formen) Deutsche Ztschr f. Nervenh 96 38, 927

[illegible] Barrett, A M Hereditary Occurrence of Hypothyroidism With Dystrophies of the Nails and Hair Arch. Neurol & Psychiat 2: 628, 1919.

[illegible] Reuter M J Histopathology of the Skin in Myxedema, Arch Derma & Syph 24 55 1931

[illegible] Freudenthal, W and Brinsner St R. Myxoedema papulosum et annulare Proc Roy Soc. Med. 35: 355-360, 1942.

myxedematous in appearance and histology but are in the majority of the cases associated with hyperthyroidism even with the fully developed syndrome of exophtalmic goiter It seems as if in these cases some parts of the skin especially of the lower legs are unable to use the hormone which is offered in abundance



Fig 17



Fig 173

Fig 174 —Circumscribed [illegible] myxedema (Courtesy Division of Dermatology Department of Medicine University of Chicago)

Fig 17 Myxedema [illegible] (Courtesy Dr M Jessner)

The lesions are hard nodules or tuberous plaques of varying size sometimes covering both pretibial areas They are symmetrical and may be normal in color yellowish pinkish or brownish Inflammatory symptoms are mostly absent The follicles are often dilated so that a pig skin or orange peel appearance result The lesions are quite hard and nonpitting Hypertrichosis within the lesion is another paradoxical feature which has been encountered [illegible] The sweat secretion within the myxedematous lesion [illegible] normal or absent.[illegible] The tempera

[illegible] Richter W Lokales [illegible] symmetrisch [illegible] beiden [illegible] bei Kranker mit Basedo Zbl 42 471 1932

[illegible] Ingram, J T [illegible] Myxedema Associated With Hyperthyroidism, Rev [illegible] 1932 Zbl 41 756 1933

ture may be much lower than in the normal skin.[illegible] On puncture a mucilaginous tenacious serum seeps from the wound The microscope shows infiltration with masses and strands of mucin

The major changes are found in the cutis. The connective tissue fibers are edematous and homogenized Oval and stellate cells are scattered throughout.[illegible] Treatment with thyroid or iodine has occasionally produced toxic symptoms Thyroidectomy precipitated the outbreak of circumscribed myxedema in some cases but abolished it in others. Since this dermatosis causes little discomfort, the treatment should be guided by the necessities of the general condition [illegible]



Fig. 176 Myxedema [illegible] with hyperkeratosis. From Auerbach J. O. Arch. Dermat. & Syph. [illegible]

Lichenoid umbilicated papula [illegible] tuberous placque-like and other varieties of discrete myxedema are known as the atypical myxedema of Jadassohn and Doesekker [illegible] The connection with thyroid dysfunction is usually less obvious

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[illegible] Carol, W. L. L. Atypisches Myxoedem. Nederl. Tijdschr. v. geneesk. 75 4156-4160 1931 Zbl. [illegible] 753

[illegible] O'Leary P. A. Localized Solid Edema of the Extremities in Association With Exophthalmic Goiter Arch. Dermat. & Syph. 21 770 1930

[illegible] O'Leary P. A. Solid Edema of the Face Arch. Dermat. & Syph. 21 330-331 1930

[illegible] Haines [illegible] F. Exophthalmic Goiter and Myxedema, Endocrinology 12 [illegible] 1928

[illegible] Doesekker W. A. [illegible] Myxoedem, Arch. f. Dermat. [illegible] Syph. 123 76 1916

in this group than in diffuse or pretibial myxedema [1301] The oral mucosa may be involved [1302]

Temporary facial puffiness following subtotal thyroidectomy but different from the localized form of myxedema has been observed in nine cases.[1303] It seems to be a mild form of myxedema and responds to thyroid therapy

The Parathyroid Glands

The hormone of the parathyroid glands is concerned with calcium metabolism It maintains the level of ionized calcium in the blood and regulates the use of calcium for skeletal growth The proper degree of nervous and muscular irritability and the viscosity and coagulation of the blood are also influenced by the presence of calcium

Relations between the parathyroids and certain dermatoses have often been suspected (see scleroderma calcinosis) but our knowledge of the skin in hyperparathyroidism is meager and uncertain Albright[1304] in his work on hyperparathyroidism does not mention any skin changes and no mention is made in the review of 135 proven cases by Wilder and Howell [1305]

Hypoparathyroidism

Extirpation of the parathyroids was in a number of cases followed by the outbreak of a severe and characteristic dermatosis clinically identical with impetigo herpetiformis (Hebra) Since other symptoms of insufficient parathyroid activity especially tetany have been found in spontaneous cases of impetigo herpetiformis it seems justified to regard this disease as a dermadrome of hypoparathyroidism

Impetigo Herpetiformis—Hebra[1306] in 1872 and shortly after him Kaposi [1307] first described the clinical picture of this disease and it has been but little changed since The dermatosis starts with crops of pustules which often appear during pregnancy but sometimes in women without relation to pregnancy or in men The primary lesion is a true pustule i e a vesicle filled with pus from the beginning and has a red and swollen base. These pustules are the size of a pinhead and are superficially seated in the epidermis being grouped in clusters and lines. Confluent pustules in the center of such groups form a scab (impetigo) while new pustules develop at the periphery and the center heals under the scab forming rings and polycyclic figures.

These eruptions may cover large areas sometimes the whole body surface The navel the genital and inguinal areas the armpits and the submammary

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[1303] Thompson and Thompson Temporary Edema of the Face Following Treatment for Exophthalmic Goiter Am J M Sc 178 73 1929

[1304] Albright, F A b, J C and Bauer W Hyperparathyroidism, J A M A. 102 1276-1287 1934

[1305] Wilder R M and Howell, L P Etiology and Diagnosis in Hyperparathyroidism A Review of 135 Proved Cases J A M A 106 427-431 1936

[1306] Hebra, F Ueber einige in der Schwangerschaft und bei Uterinalkrankheiten der Frau beobachtet Hautkrankheiten, Wien. med Wchnschr 1872.

[1307] Kaposi, M Impetigo herpetiformis, Arch f Dermat. & Syph 19 273-296, 1887

regions are usually first and most severely involved Deep ulceration has not been seen Sometimes the mucosa shows lesions analagous to those of the skin. Crops of new pustules are often accompanied by chills and fever Nephritis splenomegaly and cachexia are the rule in fully developed cases which may take on the aspect of generalized exfoliative dermatitis. Itching is not a dominant symptom.

Impetigo herpetiformis is a severe and often fatal disease Of the thirteen patients with impetigo herpetiformis reported by Kaposi[illegible] from 1872 to 1884 twelve died from the disease. Glävecke[illegible] (1896) found a mortality of 80 per cent among 20 cases from the literature During the last twenty years relatively many nonfatal cases have been reported

This disease is so rare that many dermatologists have never seen it. The great interest which it aroused is due to the fact that it is a characteristic dermatosis with a definite endocrine relationship Hebra[illegible] and Kaposi[illegible] who saw more cases than any other writers were convinced that impetigo herpetiformis is a disease of pregnant women Later on Kaposi described a case in a man and more recently several cases in nonpregnant women in children and in men[illegible] have been presented

In 1921 Schardorn[illegible] reported two cases of impetigo herpetiformis and tetany in nonpregnant women who only three days before had been subjected to thyroidectomy Both women died and at autopsy no parathyroids were found If there was any doubt about the part the operation played in the etiology it has been removed by the publication of at least nine more cases following thyroidectomy [illegible] In a case published by Kolisch [illegible] tetany followed thyroidectomy The patient later became pregnant and developed impetigo herpetiformis. On the other hand it is surprising that impetigo herpetiformis has not been seen more often among th many cases of total thyroidectomy Kocher [illegible] e.g in his f mous paper in 1906 does not mention impetigo herpetiformis as a symptom of cachexia following total strumectomy

The spontaneous cases in pregnancy are often but not always associated with symptoms of hypoparathyroidism Osteomalacia tetany [illegible] low

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[illegible] Glävecke Impetigo herpetiform. Arch f. Gynaek. [illegible] 15-34 1896

[illegible] Hall A F Impetigo herpetiformis in Male, Arch Dermat & Syph. [illegible] 107 12, 1944.

[illegible] Schardorn Impetigo herpetiformis. Arch f Derma Syph. [illegible] 108-130, 1921.

[illegible] Lutz Impetigo herpetiformis. Derma Ztschr [illegible] [illegible]-300, [illegible]

[illegible] Kapp Dermatitis para hyreopriv unter dem Bilde der Impetigo herpetiformis. Zbl [illegible] 132, [illegible]

[illegible] Hartmann, J Zur [illegible] Therapie der Impetigo herpetiformis, Arch f. Dermat. & Syph 175 [illegible]-106, [illegible]

[illegible] Wise F Dermatitis herpetiformis Appearing Three Weeks After Thyroidectomy Arch Derma & Syph 27 [illegible], [illegible]

[illegible] Schmidt LaBaume Impetigo Herpetiformis and Cure With A T 10 (Dihydrotachysterin Holtz) Med Klin [illegible] 1000 1937

[illegible] Schubert M Impetigo Herpetiformis A. T 10 Therapie Derma Wchnschr [illegible] 76 [illegible]

[illegible] Daniels, E Impetigo herpetiformis, postoperative Tetanie parathyreoprive Kachexie, Frankfurt Ztschr f Path [illegible] [illegible] [illegible]

[illegible] Wertheimann, A Ueber Impetigo herpetiformis Hebrae Arch f Dermat Syph. 157 214-233 1929

[illegible] Kolisch, E Impetigo herpetiformis, Zbl f Gyn 48: No. [illegible]

[illegible] Kapferer Ueber Impetigo herpetiformis und Schwangerschaft, Zbl 11 3 9 1934

[illegible] Lewczynski Impetigo herpetiformis. Zbl. 43 [illegible] [illegible]

serum calcium[illegible] and cataract[illegible] have been observed with impetigo herpetiformis in pregnancy but a considerable number of cases have been found free of all such symptoms This together with the nonobligatory occurrence after parathyroidectomy suggests that hypoparathyroidism is only one of the pathogenetic factors. In which direction other factors may be sought is indicated by cases with pituitary findings,[illegible] mediastinal tumor[illegible] and dysfunction of the ovaries.[illegible] The possibility of an infection which only develops under certain circumstances cannot be denied though the lesions and the blood have almost always been found sterile Italian authors have lately suggested a virus infection



Fig 177 Female aged 21 years [illegible] infection of nails hands feet and [illegible] with Monilia albicans in case of [illegible] bilateral cataract and hypertension (Courtesy Wiscons[illegible] General Hospital

under certain hormonal and toxic conditions.[illegible] The clinical similarity to pustular psoriasis must be mentioned since hypocalcemia seems to be an etiological factor in this dermatosis also

The impetigo herpetiformis of pregnancy brings up the question of the artificial termination of the pregnancy in the case of this disease Several dermatologists feel that this procedure is justified However the disease not infre-

[illegible]Carter B and Pearse R L Impetigo Herpetiformis Occurring During Pregnancy Am J Obst & Gynec 33 [illegible] 1937

[illegible]Korbs A O Hypocalcinosis Arch f Derma Syph 179 [illegible] 1939-1940

[illegible]Tryb A Beitrag zur Aetiologie der Impetigo herpetiformis Arch f Derma Syph [illegible] 407-411 1921

[illegible]Buschke A Impetigo Herpetiformis [illegible]

[illegible]Buschke A Impetigoherpetiformis[illegible] Hautaffection bei [illegible] Dermat Wchnschr 78 [illegible] 1924

[illegible]Zocchi Impetigo erpetiforme in [illegible] Ginecologia [illegible] 1930

quently starts in the later months of pregnancy when inducing labor in the presence of a widespread purulent skin infection is a dangerous procedure. Moreover the termination of pregnancy does not always influence the course favorably In some cases the patients died from the dermatosis during the puerperium. Nevertheless, if the diagnosis is made early the pregnancy should be terminated and future pregnancies prevented [illegible]

There have been almost as many methods of treatment tried as cases recorded Blood transfusions [illegible] injections of normal serum and of serum of normal pregnant women [illegible] estrogenic hormone (Buschke) and X ray sterilization[illegible] have been used Sulfanilamide accomplished a spectacular recovery in one recent case [illegible] Calcium in large doses[illegible] should always be given In tetany Sevringhaus [illegible] advises the oral administration of a 35 per cent solution of calcium chloride in a sweet vehicle one to two teaspoonfuls three times daily The medicine is given one-half hour before meals with plenty of water Parathyroid extracts are unreliable Dihydrotachysterol [illegible] a derivative of ergosterol also known as A.T 10 is more promising There are a number of favorable reports on record [illegible] The dose is five to twenty drops of the oily solution daily [illegible] A.T 10 is so far the best substitute for the parathyroid hormone. It increases the phosphorus excretion and raises the calcium level of the blood

Parathyroid insufficiency seems to increase the susceptibility to *chronic monilia infections* of the hands and nails.[illegible]

Brittleness of the nails and hairs together with hyperhidrosis and Addisonoid hyperpigmentation is occasionally associated with hypoparathyroidism [illegible]

The Thymus

Status thymicolymphaticus of the adult is a much disputed condition The beard and body hair has been described as scanty and there often is a female configuration in men [illegible] Scantiness of the beard and of the axillary and pubic hair in both sexes with heterosexual distribution is part of Timme s syndrome which is a chronic multiglandular benign condition with pituitary gigantism low blood pressure low blood sugar and other features.[illegible]

[illegible] Buschke A and Curth W Die Bedeutung der Graviditätsdermatosen für die künstliche [illegible] Schwangerschaft. München med Wchnschr 76 [illegible] 1929

[illegible] Scherber G Zur Behandlung der Impetigo herpetiformis der verschiedenen Pemphigusformen und [illegible] multiformer Erytheme [illegible] in der Dermatologie Wien med Wchnschr [illegible] 1930

[illegible] Rotow Impetigo herpetiformis Zbl [illegible]

[illegible] Rotow P L [illegible] Fälle von Impetigo herpetiformis, Derm Wchnschr 91 [illegible] 1930

[illegible] Grütz Impetigo herpetiformis Zbl [illegible]

[illegible] Frank L J Impetigo Herpetiformis Arch Dermat & Syph. [illegible] 1939

[illegible] Hall F [illegible], Deutsche med Wchnschr [illegible] 1930

[illegible] Scherber G Zur Klinik und Aetiologie der Impetigo herpetiformis, Wien med Wchnschr [illegible] 1930

[illegible] Albright F and McCune D J Five Cases (Three in Siblings) of Idiopathic Hypoparathyroidism Associated With Moniliasis J Clin Endocrinol [illegible] 1943.

[illegible] Emerson H Status Lymphaticus in Adults Arch. Int Med. [illegible] 1914.

[illegible] Wolf W Endocrinology in Modern Practice Philadelphia, [illegible], W B. Saunders Company

Carcinoma of the thymus has been seen to produce Cushing's syndrome in at least 3 cases.[1339-1341] The "juvenile Hercules" syndrome of precocious puberty in the male was seen in a case of mediastinal tumor, probably a thymus lesion.[1342] Most thymomas do not provoke dermadromes.

Deficiency of the thymus has by several authors been thought to be a cause of *psoriasis*. The hypothesis was based on therapeutic results with injections of thymus extract[1343] and stimulating doses of roentgen radiation directed to the upper sternal region.[1344, 1345] Little has been heard of the subject during the last fifteen years.

[1339] Layton, O., Turnbull, H. M., and Bratton, A. B.: Primary Cancer of the Thymus With Pluriglandular Disturbance, J. Path. & Bact. 34: 635, 1931.

[1340] Duguid, J. B., and Kennedy, A. M.: Oat-cell Tumors of Mediastinal Glands, J. Path. & Bact. 33: 93, 1930.

[1341] Thompson, K. W., and Eisenhardt, L.: Cushing Syndrome, J. Clin. Endocrinol. 3: 445-452, 1943.

[1342] Weber, E. P., and Wohl, M.: Macrogenitosomia of "Juvenile Hercules" Type With Tumor in Superior Mediastinum, M. Press 211: 23-26, 1944.

[1343] Samberger, J.: Ueber das Wesen der Psoriasis, Acta dermat. venereol. 2: 359, 1921.

[1344] Brock, W.: Beziehungen der inneren Sekretion zur Schuppenflechte und deren Behandlung mit Thymusbestrahlung, Strahlentherapie 11: 563-604, 1920.

[1345] Brock, W.: Psoriasis und innere Secretion, Deutsche med. Wchnschr. 47: 1420-1422, 1921.

CHAPTER XVIII

DISORDERS OF THE ENDOCRINE GLANDS

THE ADRENAL GLANDS

The adrenal cortex through its hormone cortin is concerned with water mineral and carbohydrate metabolism [1296] It keeps up the muscular strength and it has important functions in pregnancy and lactation. Androgenic substances which are able to masculinize the appearance of females are produced in the adrenal cortex or in its neoplasmas. The medulla of the adrenal glands produces adrenalin which besides other effects stimulates the sympathetic system and inhibits the vagus Destruction of the adrenals is fatal

Addison s Disease

Addison s disease[1297] starts insidiously usually in middle life Progressive asthenia and muscular fatigability hypotension epigastric pain anorexia morning sickness and other gastrointestinal symptoms may after long periods of relative mildness, suddenly increase and give rise to an acute condition known as Addisonian crisis. Hyperpigmentation of the skin is an outstanding symptom Dehydration decrease in the sodium and chlorine concentration in the blood increase in the blood potassium and nonprotein nitrogen (urea) and hypoglycemia are important findings especially during the crisis The urinary sodium chloride is high Sugar may occur in the urine in spite of the hypoglycemia [1299] The blood viscosity is high Anemia is marked. The elimination of water after a sudden large intake of water is delayed A water test designed by Robinson Power and Kepler [1298] together with blood and urine chemistry has lately been shown to be of great diagnostic value [1298] The course is almost always fatal but with modern treatment health may be restored to such a large measure that cure may seem to be accomplished yet sudden death may occur from trivial causes [1300] The cause of the syndrome is destruction of the adrenal cortex *due in 9 out of 10 cases, to tuberculosis*

[1296] Goldzieher M A The Adrenal Glands in Health and Disease Philadelphia, 1944 F A Davis Company

[1297] Addison T A Collection of the Published Writings of the Late Thomas Addison on the Constitutional and Local Effects of Disease of the Suprarenal Capsules New Sydenham Society 1868. Reprinted in Rowntree and Snell Addison's Disease Philadelphia, 1931 W B Saunders Company

[1298] Robinson, F J Power M H and Kepler E J Addison's Disease—Diagnosis, Proc Staff Meet Mayo Clin 16 577-583, 1941

[1299] Cutler M H Power M H and Wilder R M Concentrations of Chloride Sodium and Potassium in Urine and Blood Their Diagnostic Significance in Addison Disease J.A.M.A. 111 117 122, 1938

[1300] Rowntree, L G Report of 3 Cases of "Clinical" Addison's Disease Surviving More Than 15 Years Endocrinology 26 793-800, 1940

Carcinoma of the thymus has been seen to produce Cushing's syndrome in at least 3 cases.[1389-1391] The "juvenile Hercules" syndrome of precocious puberty in the male was seen in a case of mediastinal tumor, probably a thymus lesion.[1392] Most thymomas do not provoke dermadromes.

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[1389] Leyton, O., Turnbull, H. M., and Bratton, A. B.: Primary Cancer of the Thymus With Pluriglandular Disturbance, J. Path. & Bact. 34: 635, 1931.

[1390] Duguid, J. B., and Kennedy, A. M.: Oat-cell Tumors of Mediastinal Glands, J. Path. & Bact. 33: 93, 1930.

[1391] Thompson, K. W., and Eisenhardt, L.: Cushing Syndrome, J. Clin. Endocrinol. 3: 445-452, 1943.

[1392] Weber, E. P., and Wahl, M.: Macrogenitosomia of Juvenile Hercules Type With Tumor in Superior Mediastinum, M. Press 211: 23-26, 1944.

[1393] Samberger, J.: Ueber das Wesen der Psoriasis, Acta dermat. venereol. 2: 330, 1921.

[1394] Brock, W.: Beziehungen der inneren Sekretion zur Schuppenflechte und deren Behandlung mit Thymusbestrahlung, Strahlentherapie 11: 563-604, 1920.

[1395] Brock, W.: Psoriasis und innere Secretion, Deutsche med. Wchnschr. 47: 1420-1422, 1921.

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[1946] Goldzieher M A The Adrenal Glands in Health and Disease Philadelphia, 1944, F A. Davis Company

[1947] Addison, T A Collection of the Published Writings of the Lat Thomas Addison on the Constitutional and Local Effects of Disease of the Suprarenal Capsules. New Sydenham Society 1868 *Reprinted in Rev tree and Snell Addison's Disease, Philadelphia, 1931 W B Saunders Company*

[1948] Robinson, F J Power M H and Kepler E J Addison's Disease—Diagnosis, Proc. Staff Meet., Mayo Clin 16: 577-583 1941

[1949] Cutler M H Power M H and Wilder R. M Concentrations of Chloride Sodium and Potassium in Urine and Blood Their Diagnostic Significance in Addison's Disease J.A.M.A. 111: 117 122, 1939

[1950] Rowntree L G Report of 3 Cases of "Clinical Addison's Disease Surviving More Than 15 Years Endocrinology 26: 793-800, 1940



Fig. 178.—Addison's disease. Patient (left) with her sister for comparison. Discoloration only complaint so far. Patient died five months later.



Fig. 179.—Addison's disease. Note pigmentation of exposed part. (Courtesy Wisconsin General Hospital.)

Dermadromes.—*Hyperpigmentation* of the skin in connection with destructive adrenal disease is in the vast majority of cases an early symptom often appearing before asthenia and fatigability. Pigmentation about the knuckles may be the first manifestation.[illegible]

The fully developed discoloration is uneven in distribution and color. The face, neck, hands, and other light exposed parts, the normally pigmented areas, the nipples, the linea alba of women who have been pregnant, the genital region, the gluteal fold and the umbilicus are usually affected first. All areas subject to



Fig. 80.—Addison's disease. Note pigmentation in belt area and over prominent bones. (Courtesy Wisconsin General Hospital.)

pressure, friction, and irritation are apt to take on a darker color than the rest of the skin. Thus girdles, garters, shoulder straps, collars, collar buttons and bandages may leave indelible marks. The author saw a deaf woman who was wearing a hearing aid apparatus, the cord of which ran along her back. The slight pressure and friction of this cord had left a deep pigmented mark in the skin at a time when there was hardly any asthenia and little other pigmentation. The creases of the palms and the wrists are sharp dark lines, while the palms themselves are still light. Tight skin over bones is often hyperpigmented. Scars, e.g., vaccination marks, have a pronounced tendency to darken early in Addison's

[illegible] Rowntree, L. G., and Snell, A. M.: A Clinical Study of Addison's Disease, Philadelphia, 1931, W. B. Saunders Company, p. 176.

[illegible] Snell, A. M., and Rowntree, L. G.: Addison's Disease With Anomalous Pigmentation, Endocrinology 8: 363, 1929.

Fig. 181.



Fig. 182.

Fig. 181.—Addison's disease. Pigmentation of palmar creases.
Fig. 182.—Addison's disease. Pigmentation of scars (flat iron burns).

disease Spillmann[1353] advises to watch for the development of pigmentation after the application of an irritant plaster of mustard seed. Besides the unevenness caused by the various terrains, great differences in the intensity of the pigmentation occur. In some cases the discoloration is blotchy, in others irregular and ill defined. Some cases present patterns which look like a geographical map, especially if much depigmentation accompanies the pigment increase. Thus pictures resembling vitiligo may ensue. True vitiligo has often been seen together with Addison's disease[1353] and it is interesting that hypotension has been found in a number of vitiligo cases.



Fig. 183.—Addison's disease. Deep hyperpigmentation and depigmentation surrounding the area. White patient.

Leukoderma acquisitum centrifugum (Sutton's disease) and vitiligo have been seen in one case of Addison's syndrome.[1354] Some areas of the skin offer a marked resistance to the pigmentation. The narrow strip surrounding the lips often stays pale even in extremely dark pigmented cases. The same is sometimes true of the fingertips and nailbeds and the backs of the hands, to a certain extent also of the eyelids. The circumoral strip often remains relatively white in other pigmentations as well, for example in the form of discoloration which has been described by Poor[1357] as chloasma periorale virginum.

The color of the Addison melanoderma is most commonly a tan[181] but may vary from slate, amber or brown shades to the dark black of a full blooded Negro. This latter, however, is very rare. The depigmentation of the circum-

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[1353]Spillman, L. Dermatoses en rapport avec des troubles des glandes endocrines et de la nutrition, Nouvelle Pratique Dermatologique. Vol. 3, Paris 1936, Masson & Cie. pp. 644-731.

[1354]Obermayer, M. E. Leukoderma Acquisitum centrifugum and Vitiligo in Patient With Addison's Disease. Arch. Derma. & Syph. 35: 320, 1937.

PLATE III

1 Addison's disease. Advanced case

2 Addison's disease. Pigmented palmar creases.

3 Addison's disease. Pigmentation of the tongue.

4 Addison's disease. Pigmentation of the gums.

5 Hemangioma of pregnancy. Recurring in several pregnancies and receding spontaneously after childbirth. (Patient of Dr J Barrock.)

6 Kraurosis vulvae, multiple carcinomas.





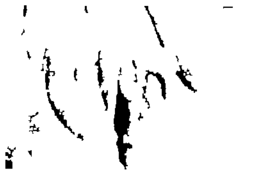



PLATE III

Fig 194.



Fig 1[illegible]



Fig [illegible]



Fig [illegible] — Addison's disease Pigmentation of labial mucosa.
Fig 1[illegible] Racial pigmentation of oral mucosa.
Fig [illegible] — Addison's disease Pigmented spot in gum.

oral area and of the nailbeds is most striking in such cases. Jet black freckles are often seen mainly in areas exposed to light but even in unusual places like the palms and soles.[1311]

The lips and the oral mucosa almost always show quite sharply outlined slate or bluish spots sometimes streaks. They resemble those seen in the mouth of the Negro They appear rather early in the labial buccal or palatal mucosa sometimes on the tongue. The conjunctivae and the sclerae of the eyes as well as the vagina may participate in the general hyperpigmentation. Melanosis of the rectal mucosa has not yet been demonstrated A number of cases of Addison s disease in the Negro have been recorded. Here the Addisonian pigment may be superimposed on the natural pigment so that the palms and soles become darker and an extremely dark color of the rest of the skin results.

Montgomery and O Leary[1312] emphasizes the relative softness of the skin which he relates to the flattening of the rete ridges and the thin but not atrophic epidermis Sweating is often pronounced Some believe the sweat to have a fishlike odor [1313] In prolonged cases the hair may become darker particular coarseness or hypertrichosis is denied [1314] Premature graying and scantiness of the hair has been observed in the course of the disease [1316, 1317] The frequent shedding of the axillary and pubic hair is emphasized by Albright.[1318] The nails may rarely take on a yellowish hue Usually they stay pale [804]

Histopathology and Pathogenesis —The pigment is melanin and as such it is free of iron It is accumulated in the tops of the basal cells of the epidermis. Dendritic chromatophores are also found in the cutis.[1315] Bittorf[1319] tried to explain the pigmentation in Addison s disease by assuming a higher oxidase content in the skin His experiments with the skin of patients with Addison s disease were not confirmed by B Bloch[1320] and his school who believed that not the increased oxidase content of the skin but an increased amount of melanogens accounts for higher melanin production It was suggested that in the disturbed adrenals less tyrosin might be changed into adrenalin and thus more tyrosin might be available as a promelanin Later (1928) Szent-Györgyi[1321] who isolated vitamin C from normal adrenals advanced the theory that the high reducing power of this substance (then called hexuronic acid) serves as a control in the *oxidation of promelanin to melanin in the normal skin* *Its deficiency* caused by destruction of the cortex would increase the oxidizing power of the skin and thus enhance the melanin formation which is an oxidation process. A great deal of experimental work seems to corroborate the antipigmentogenic role of vitamin C

[1312] Montgomery H., and O Leary P A Pigmentation of the Skin in Addison Disease Acanthosis Nigricans and Hemochromatosis, Arch Dermat. & Syph 21 970-984 1930

[1313] Bauer Julius Innere Sekretion Berlin, 1927 Julius Springer

[1314] MacBryde, C M Addison Disease M Clin North America 26 391-400, 1942.

[1318] Albright F Smith, P H and Fraser R Syndrome Characterized by Primary Ovarian Insufficiency and Decreased Stature Tr A Am Physicians 57 219-226, 1942

[1319] Bittorf Pathologie der Nebennierenerkrankungen, Jena, 1908, O Fischer Ueber die Pigmentbildung bei der Addison schen Krankheit München. med Wchnschr 70 230-232, 1923

[1320] Bloch, B and Löffler W Untersuchungen über die Bronzefärbung der Haut bei der Addison schen Krankheit Deutsches Arch f klin Med 121 262-301 1917

[1321] Szent -Györgyi A Observations on Function of Peroxidase Systems and Chemistry of Adrenal Cortex Description of New Carbohydrate Derivative Biochem J 22 1387 1409 1928 also On the Chemistry of the Adrenal Cortex Am J Physiol 90 536 1929

It is well known that lemon juice which has a high vitamin C content prevents the blackening of cut surfaces of fruit e.g avocado pears and inhibits the oxida tive dopa reaction [illegible] Vitamin C is also able to bleach pigmentations including those of Addison s disease

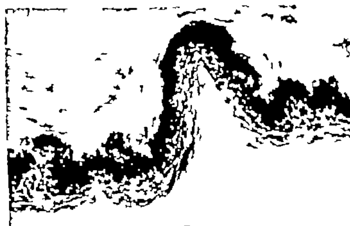


Fig 107 — Addison disease (Courtesy Division of Dermatology Department of Medicine, University of Chicago)

Pigmentation of the skin and melanogen formation in the urine after exposure to light can be inhibited by previous administration of vitamin C [illegible] W Jadassohn and Schaaf [illegible] however showed that even large amounts of vitamin C could not prevent the pigmentation produced in guinea pigs by estrogens, and other authors[illegible] believed that the concentration of vitamin C in the human serum would not be strong enough to inactivate the dopa oxidase and to inhibit the dopa reaction as it does in vitro In this connection the vitamin C deficiency in pregnancy which is a period of increased pigment formation may be mentioned

The theory of the pigmentation inhibiting power of vitamin C would be in line with Bittorf's[illegible] opinion that it is the higher oxidizing power and not the higher amount of melanogen which causes the Addisonian pigmentation

Szent Györgyi [illegible] in accordance with Bloch and Löffler's[illegible] work, tried to link the theories by suggesting that vitamin C deficiency which also leads to decreased production of adrenalin might thus keep more melanogen available for production of melanin Adrenalin is closely related to several of the melan ogens (pyrrol tyrosin dopa etc) If this double pigmentogenic role of vitamin C should be confirmed it might help to explain the high degrees of pigmentation reached in Addison disease

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[illegible] Stepp, W Kühnau, J and Schroeder H Die Vitamine Stuttgart, 1936 Ferdinand Enke

[illegible] Schade H A. Beitrag zur Frage des Einflusses von Vitamin C (l Ascorbinsäure) auf Pigmentierungsvorgänge Klin. Wchnschr 14 60-61 1935.

[illegible] Kahler H and La Croix, Y Ueber den Einfluss der Ascorbinsäure auf die Melanogenausscheidung, Klin Wchnschr 14 1031 1032, 1935.

[illegible] Jadassohn, W and Schaaf, F Depigmentierende Wirkung der l-Ascorbinsäure (Vitamin C) Klin Wchnschr 13 645-646, 1934

[illegible] Fasll, P and Fessler A Vitamin C and Dopareaktion, Klin. Wchnschr 14 876-877 1935

Hyperpigmentation has been observed in true scurvy This observation could be used as another argument in favor of the vitamin C theory of the Addisonian pigmentation Difficult to reconcile with the outlined role of vitamin C is the observation that this substance occurs together with melanin in the human skin [1327] Lately (Edelbacher and Zeller quoted by Robert and Zeller[1328]) the experimental formation of melanin from histamine by the enzyme diamin oxydase (DO) has opened a new path In adrenalectomized animals the formation of the histamin decomposing enzyme DO is disturbed But not more than this hint of a relationship has so far been given A definite explanation of the pigmentation in Addison s disease has not yet been found

Recently the role of the sympathetic system in the pigment formation in Addison s disease has again been emphasized [1329] The disturbance of the sympathetic system caused by the destruction of the adrenal cortex may lead to melanosis Hyperpigmentation due to destruction of the plexus coeliacus and other sympathetic structures by neoplasms aneurysms or injuries is well known[1329] see also acanthosis nigricans nervous system

Treatment —The treatment of the pigmentation in Addison s disease has hardly been tried by other methods than those directed towards the adrenal insufficiency Four important advances have been made during the last decade [1330] These are (1) the introduction of salt therapy (2) the restriction of potassium salts (3) the elaboration of potent extracts of the adrenal cortex and (4) the synthesis and availability of desoxycorticosterone esters It seems as was to be expected that their value is due to the fact that they maintain life not that they cure the destructive process in the adrenal cortex just as insulin does not cure diabetes. In spite of the sometimes dramatic effect on most of the symptoms [1331] the fully developed pigmentation is hardly ever reversed This opinion of investigators who treated many cases of Addison s disease is in contrast to other reports. [13, 1331-1332] Dehydration in times of remission and while under treatment with desoxycorticosterone and salt may make the patient appear lighter in color The pigmented spots in the mouth will rarely disappear under any form of treatment.[1333] In the rare cases of syphilitic Addison s disease complete disappearance of all symptoms including pigmentation has been seen But unfortunately the vast majority of the cases of Addison s syndrome are due to tuberculosis.

Some metabolic parallels of adrenal insufficiency and pemphigus especially the lowering of the chloride and protein level and the increase of the plasma volume and interstitial fluid have led to encouraging trials of desoxycorticosterone acetate

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[1327] Cornbleet T Vitamin C and Pigment Arch Derma & Syph 35 471-479 1937

[1328] Robert P and Zeller E A Pigment Formation and Diamine Metabolism Rôle of Dopa Oxidase, Sch eiz med W hnschr 71 1006-1007 1941

[1329] Vos K p. T Hau melanose ed Nebennieren Virchows Arch f pa h Anat 309 311-317 1942

[1330] Loeb, R F Adrenal Insufficiency Bull New York Acad Med 16 340-347 1940

[1331] Rowntree L G Results of Treatment i Addison Disease M Clin North America 24 1779-1787 1940

[1332] Moury A Pathogénie et ... ologie des mélanodermies d type addisonien, Presse méd 29 791 1921

[1333] Loeb, R F Adrenal Cortex Insufficiency J A M A 116 2495-2500 1941

(doca) in pemphigus.[1234, 1235] The recommended dose is 5 mg. 3 times daily for 3 weeks and 5 mg. daily thereafter. Autoptic findings of severe adrenal lesions in pemphigus have been reported by Goldziher.[1236]

Adrenal Tumors and Hyperplasias

Adrenal cortical tumors and hyperplasia of the adrenal cortex produce a syndrome which has received several names. Hirsutism,[1237] which refers to the main feature of hypertrichosis, is most often used. Other terms are hyper adrenalism, genitosuprarenal syndrome and genitosuprarenal virilism. The term interrenalism[1238, 1239] refers to the interrenal organ of the elasmo-branch fishes which instead of adrenals have an elongated body between the kidneys, closely resembling in its histology the mammalian adrenal cortex. Lately the syndrome of rapidly acquired obesity of the trunk, kyphosis and round shoulders, striae, dusky skin and hirsutism, amenorrhea or impotence, hypertension and fatigability has often been referred to as Cushing's syndrome[1240] even if it is not associated with Cushing's disease, basophil adenoma of the pituitary. Primary adrenal tumors of the cortex as well as of the medulla are very rare. Gibson[1241] found only one in approximately 12 000 admissions to the University of California Hospital.

The adrenal cortical tumors or hyperplasias which produce the syndrome of hirsutism occur in females in 80 per cent of the cases. A considerable number has been found in young children, even in the newborn.[1242] The cortical neoplasms observed so far have been carcinomas, benign adenomas, sarcomas and metastatic growths from cancer of the breast or of the stomach. The localization in the cortex rather than in the medulla is more important in the production of a typical syndrome than the histology of the tumor. Very small adenomas may cause fully developed hirsutism. No parallelism exists between the size of the neoplasm and the degree of the syndrome. The hyper nephromas (Crawitz tumors) do not cause hirsutism. In several instances highly malignant cortical neoplasms were found without having produced the syndrome of hirsutism[1243] (Wu quoted by Kepler and Keating[1244])

Dermadromes.—The syndrome caused by adrenal cortical tumors is modified by sex and age. In small boys precocious puberty with enlargement of the

[1234] Talbott, J. H., and Coombs, F. S. Pemphigus, Arch. Dermat. & Syph. 42: 249-269, 1940.
[1235] Goldman, A., Markham, M. J., and Schaffer, A. J. Case of Pemphigus Treated With Desoxycorticosterone Acetat, J. Clin. Endocrinol. 2: 343-344, 1942.
[1236] Goldziher, J. W. Adrenal Glands in Pemphigus Vulgaris, Arch. Dermat. & Syph. 53: 43-44, 1946.
[1237] Apert, E. Sur l'hirsutisme, Bull. et mém. Soc. méd. d. Hôp. de Paris 41: 181, 1925.
[1238] Mathias, E. Ueber Andeutungsformen von Interrenalismus, Zentralbl. f. Gynäk. 50: 2150-2152, 1926.
[1239] Wright, S. Applied Physiology, New York, 1940, Oxford University Press.
[1240] Warren, F. L. Estimation of Urinary Ketosteroids in the Diagnosis of Adrenal Cortical Tumors, Cancer Research 5: 49-5, 1945.
[1241] Gibson, T. E. The Diagnosis of Adrenal Tumors With Classification of Adrenal Tumor Syndromes: Cases, J. Urol. 18: 83-90, 1927.
[1242] Bayer, C., and Lang, F. J. Ueber Macrogenesis Interrenalis Congenita, Endokrinologie 14: 225, 1934.
[1244] Kepler, E. J., and Keating, F. R., Jr. Diseases of the Adrenal Glands: II. Tumors of the Adrenal Cortex, Diseases of the Adrenal Medulla and Allied Disturbances, Arch. Int. Med. 68: 1010-1036, 1941.

penis hypertrichosis and muscular development create the type known as the infant Hercules Even paternity has been *reported* [1344] *In adult males*[1344] gynecomastia feminine habitus disappearance of the beard and a decrease in the size of the penis and testes have been observed Less than ten cases of this particular condition have been reported [1345, 1346] In small girls precocious puberty hypertrichosis obesity and virilism are the rule while in adult females amenorrhea and virilism dominate the syndrome. Sometimes even baldness of the male type and a mustache will develop The breasts decrease in size. This group is the largest. But it must be kept in mind that *these syndromes are not* pathognomonic for adrenal cortical lesions alone Similar changes have been seen in basophilic pituitary tumors various intracranial diseases hyperfunctioning gonadal tumors thymus tumor[1349] and other rare conditions (see chapter on puberty)

Hypertrichosis is the outstanding dermadrome in cortical tumors. It is an almost obligatory early conspicuous and sometimes even monstrous manifestation However it is by no means diagnostic of adrenal cortical tumor Not only does it occur in the above mentioned conditions but marked degrees of hypertrichosis are frequently seen in apparently healthy women with no symptoms of any endocrine disorder (See also chapter on Pregnancy) Hirsutism in children with adrenal cortical tumor has been *observed as early as the first year* of life even in the newborn There are reports of young children with beards pubic and axillary hair and heavy and pigmented lanugo growth of girls of nine with bushy eyebrows and of boys of the same age who had to shave daily The pubic hair growth in these cases usually resembles the male type The pubic change may be unilateral.[1350] High urinary androgen output has been observed [1348]

In adult women hirsutism can produce the most unusual pictures You should be women and yet your beards forbid me to interpret that you are so (Macbeth I 3) This best characterizes the impression one gets of some fully developed cases. Some of the 'bearded women of the circus side shows belong to the adrenal group The pubic hair changes to the male type. The lanugo becomes pigmented and in some parts of the body over an inch in length Long pigmented hairs in the areolae of the nipples and coarse hair in the skin over the sternum and frequently on the mammae are conspicuous. Unusually long eye lashes have been seen [349] In contrast to the general hirsutism is the loss of head hair in women with adrenal cortical tumor resembling the male baldness.[1314, 1350]

[1344] Loesery J M Sex Factors of the Adrenal Gland, Endocrinology 27 511-520 1940

[1345] Kepler E F The Adrenal Glands Paper read before the Medical Society of Milwaukee County Nov 21 1939

[1346] Holl, Cundaker 2 männliche Fälle von N bennierenrindentumoren mit innersekretorischen Störungen, Deutsche Ztschr f Chir 226 277 295, 1930,

[1348] Bissell, G W and Williams R H Hirsutism in Females, Am. Fed Cli Research (1944) 1 25-29, 1944

[1349] Dorfman, R J Wilson H M and Peters J P Differential Diagnosis of Basophilism (Cushing) and Allied Conditions Cortical Tumors and Arrhenoblastomas) Endocrinology 27 1 18, 1940

[1350] Reitter C Ein Fall mit boorm langen Cilien, Ztschr f A genk. 73 3 7 1931

[1350] Bauer J Ueberfunktion des gesamten Nebennierensystems ohne anatomischen Befund, Wien. klin Wchnschr 43, 452 546, 1930

Changes of the *pigmentation* in adrenal cortical tumors include occasional increased pigmentation around the nipple in adult males and in females pigmentation of the linea alba and the vulva comparable to that of pregnancy

Unusual *acne* and comedos either in small children or in adults is almost invariably seen in cortical tumors.[198] The acne itself often seems to differ from the typical juvenile form and resemble the severe pyodermatic type known as acne conglobata.[199]



Fig. 133 — Adrenal cortical carcinoma Hyperpigmentation. (Courtesy Wisconsin General Hospital)

The amazing symptoms of *precocious puberty* in adrenal cortical tumors have led to the publication of a great number of almost identical cases Besides the hair changes which have already been mentioned menstruation in early childhood and breast development ha e often been observed Growth of the clitoris to an erect le penis with glans corona and a hypospadic groove on the ventral surface with the labia minora shaped like a prepuce and the labia majora like a scrotum adds to the monstrosity of the syndrome Such girls may have a deep voice Th whole body of these patients may show unusual growth with or without obesity and hirsutism The infant Hercules, a sturdy little man" with unusual muscular and intellectual development and with a large erect le penis is the rare counterpart in boys The skin of the entire body is often mottled with dusky purplish red areas similar to cutis marmorata.[200] The features in precocious puberty are bloated the complexion dusky and congested

Obesity is not uncommon in cases of adrenal cortical tumor but t is more the distribution of the fat which is striking than the actual amount The com

[illegible] Wintersteiner O The Adrenogenital Syndrome J A M A. 116: 2679-2683 1941

bination of the full face the pad in the high dorsal region and the heavy abdomen together with the thin extremities creates a characteristic habitus.[illegible]

Next to the pituitary basophil adenoma cortical tumor of the adrenal is the condition which is most frequently connected with *Cushing's syndrome*[illegible]

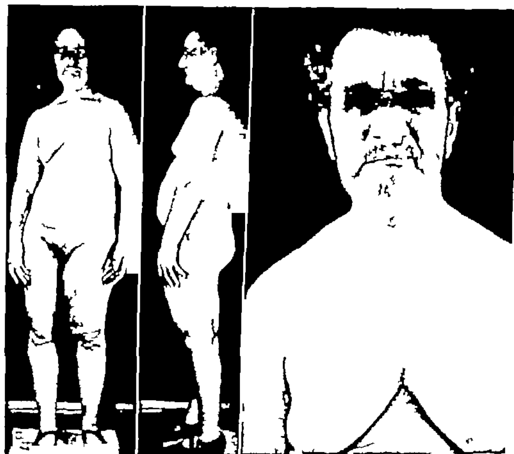


Fig 100—Achard-Thiers' syndrome (diabetes in bearded women) (From Pullen, R L and Sodeman, W A J Clin Endocrinol Courtesy of Charles C Thomas, Publisher Springfield Ill.)

Some of the cases of so-called *diabetes of the bearded women*[illegible] belong here In about 25 per cent of the reported cases hypertension amenorrhea obesity and acneiform eruptions have been noticed [illegible]

[illegible] Achard Ch and Thiers J Le virilisme pilaire et son association à l'insuffisance glycolytique (diabète des femmes à barbe) Bull Acad de méd Paris 86 51-66, 1921

[illegible] Shepardson H C and Shapiro E Diabetes of Bearded Women, Endocrinology 24 237 252, 1939

The urinary output of androgens (17 ketosteroids) is often high in adrenal cortical tumors.[1341,1384-1386] There is a general tendency to interpret Cushing's syndrome with or without pituitary adenoma as caused by hyperadreno-corticalism.[1387,1388] Striae have been seen to appear after the injection of adrenal cortical extract. The diagnosis of adrenal cortical tumor is mostly suggested by the described symptoms. But however striking they are all or some may be absent and in spite of their presence no adrenocortical tumor may be found. The similarity of symptoms in other conditions has been mentioned. The roentgenographic demonstration of cortical lesions by air injection into the perirenal fascial spaces is possible but difficult and not without danger. In recent years estrogenic and androgenic substances, substances which prolong survival of adrenalectomized animals and inactive substances which are chemically related to hormones have been found in the urine of patients with hyperfunctioning cortical lesions.[1386,341] But these findings are no more constant than other signs and symptoms. Many of the organic changes, even the monstrous symptoms of feminization and masculinization are reversible if the cortical tumor is removed. However since most of these neoplasms are malignant only few patients live long enough to experience the return of normalcy. No confirmed dermadromes have become known in tumors of the adrenal medulla.

[1384] Crooke, A. C. and Callow, R. K. The Differential Diagnosis of Basophilism (Cushing's Syndrome) by the Estimation of Urinary Androgens, Quart. J. Med. 8: 233-249, 1939.

[1385] Anderson, A. F., Hain, A. M. and Patterson, J. Adrenal Carcinoma, Hormonal Diagnosis From Excretion of Pregnanediol, J. Path. & Bact. 55: 341-349, 1943.

[1386] Hirschmann, H., and Hirschmann, F. B. Steroid Excretion in Case of Adrenocortical Carcinoma, J. Biol. Chem. 157: 601-612, 1945.

[1387] Albright, F. Cushing's Syndrome, Harvey Lect. 38: 123-186, 1943.

[1388] Anderson, E. and Haymaker, W. Cushing's Syndrome, J. Nerv. & Ment. Dis. 99: 11-430, 1944.

[1389] Herxeck, K. Ueber das Auftreten und Entstehen der Striae cutaneae distensae. Med. Welt 10: 1071-1073, 1936.

Chapter XIX

DISORDERS OF THE ENDOCRINE GLANDS

THE TESTICLES

The gonadatropic hormone of the anterior pituitary stimulates the Leydig cells in the connective tissue stroma of the testicle to produce the male sex hormone testosterone. It is excreted in the urine as androsterone which is a 17 ketosteroid. Both forms are often referred to as androgens. The international unit is the capon unit which is the biological equivalent of 100 micrograms of androsterone. Wolf[illegible] enumerates as functions of testosterone the development and maintenance of the accessory sexual apparatus, the growth and distribution of hair, the maturation of the skeleton, the larynx and the muscles, the distribution of fat, the control of libido and potency, and the determination of the masculine psychological pattern. The excretion of androgen which is only 1 to 15 I. U. per day in childhood rises at puberty to 40 to 60 I. U. in the male and 25 to 40 I. U. in the female. The reverse relationship prevails with regard to estrogenic hormone output. Beyond the age of 60 the androgens decrease[illegible] but do not completely disappear as is the case with estrogens in old women.[illegible]

The androgens are chemically only slightly different from the estrogens, cholesterol and the bile acids (see also introduction to chapter on puberty).

Many facts demonstrating the influence of the testicle on the skin of animals are known.[illegible] The best studied is the growth of the comb of the cock. Well known are the modifications of the plumage in male, female and castrated chickens. In some species, however, e.g. the guinea fowl, the plumage is not dependent on the gonads. The castrated male deer develops a "peruke," a hairy growth instead of the antlers. In the reindeer which has antlers in both sexes castration is not followed by this malformation. In the Egyptian antelope *Portas pictus* the male is gray and the female brown. The hair of the castrated male takes on the same color as the female (Zawadrosky after Sand[illegible]).

Comparable to the gonadal relations of the apocrine glands in man are the atrophy of the preputial glands in castrated mice[illegible] and of the scent glands in the male goat.[illegible] The improvement of the pelt in spayed animals[illegible]

[illegible] Dahler, F. Sexualhormonbefunde im Harn von Männern verschiedenen Alters. Ztschr. f. exper. Med. [illegible] 1933.

[illegible] Sand, K. Die Physiologie des Hodens. Hirsch. Handb. d. inneren Sekretion, vol. 2, Leipzig, 1933, Curt Kabitzsch.

[illegible] Vass, H. E. Die Präputialdrüsen der Maus in ihrer Abhängigkeit vom Hormon des Hodens. Ztschr. f. Zellforsch. u. mikr. Anat. [illegible] 1931.

[illegible] Schaffer, W. Die Hautdrüsenorgane (Hardersche Drüsen, Inguinaldrüsen, Präputialdrüsen, Analdrüsen, Kaudaldrüsen, Kieferdrüsen) der Laboratoriumssäugetiere und die Frage ihrer Abhängigkeit von den Geschlechtsdrüsen. Ztschr. f. Zellforsch. u. mikr. Anat. [illegible]

[illegible] Chatargeon. Action de la castration sur les glandes odorantes du bouc. Compt. rend. Soc. de biol. [illegible] 1931.

[illegible] Schmidt, F. Fellverbesserung durch Kastration. Klein. Tier. Pelztier. p. 232, 1931.

[illegible] Pojo, [illegible] Der Einfluss der Hypergenitalismus [illegible] auf die Produktion der Wolle und die Entwicklung der Körperformen des Schafes. Tierzüchtung [illegible] 1930.

seems to be in contradiction with the favorable effect on the fur following the administration of testosterone or transplantation of testicular tissue in senile dogs.[1367] Castration and testosterone treatment demonstrated the gonadal dependence of the striking fur characteristics of the male baboon.[1368] The pigment formation in man is also stimulated by testosterone (Milro after O Henslein 41)

The reduction of the readiness for anaphylaxis by removal of the testis and the restoration of a normal capacity for allergization by hormonal substitution has been demonstrated by Yun (after E. Urbach) The number of mitoses in the epidermis and hair follicles of the male white mouse decreases substantially after castration.[1369]

Much evidence has been accumulated suggesting a stimulating effect of androgens on number size and function of the sebaceous glands oil glands, and thickness of the epidermis[1370, 1371] and an increase of the production of prepucial smegma.[1372] Acne hirsutism obesity husky voice and enlargement of the clitoris has been observed in women who have been treated with testosterone propionate because of menstrual disturbances.[1373] Folliculitis of the nose and of other parts of the skin and acne occur sometimes in men who receive androgenic therapy

Eunuchism and Eunuchoidism

Eunuchism is the syndrome resulting from loss of the testes while eunuchoidism characterizes the state of gonadal deficiency in the male.*

Early Castration.—Loss of the testicles before puberty causes prolonged patency of the epiphyseal clefts with resulting excessive length of the extremities and fingers. The voice does not change the muscles fail to gain the masculine strength and no libido develops

Dermadromes.—Most striking is the failure to develop the sexual characteristics. The penis remains small and may be retracted into the scrotal skin which is thick and not unlike the labia majora The body hair is scanty and the beard is absent with the exception of a little lanugo on the upper lip. In later age a scanty and bristly old women's beard appears on the chin and around the angles of the mouth If there is a development of pubic hair it is of the female type The hair line along the forehead does not develop the temporofrontal

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*The terms eunuchism and eunuchoidism should be reserved for gonadal deficiencies in the male

[1367] Zahler H Rejuvenation of Senile Dogs by Means of Testicular Preparations and Their Effect on Testicles and Prostates, Virchow Arch f path. Anat 305 85-107 1939.

[1368] Zuckerman S and Parkes A. S Secondary Sexual Characters i Monkeys (Castration) J Endocrinol 1 430-49, 1939

[1369] Ortiz Picón, J M On the Effect of Castration on the Proliferative Activity of the Epidermis and of the Hair Follicles, Rev espan biol. 2 43-46, 1933 Zbl 49: 113

[1370] Hooker C W and Pfeiffer C A Growth Effects of Sex Hormones Upon Bed Growth, Skin, Hair and Sebaceous Glands in Rats, Endocrinology 32 69-76, 1943.

[1371] Rony H R., and Zakon, S J Effect of Androgen on the Sebaceous Glands of Human Skin, Arch Dermat & Syph 48 601-604, 1943

[1372] Hamilton, J B Male Hormone Substance Prime Factor J Clin Endocrinol 1 570-592 1941

[1373] Greenhill, T D and Freed, J C Virilism in Women Caused by Androgenic Therapy for Menstrual Disturbances, J A M A 112 1573-1574 1939.

notch which is to a large extent characteristic of the male. It stays straight or is *gently rounded* (see puberty) The scalp hair seems to be vigorous. The same is sometimes true of the eyebrows and eyelashes. (H Fischer after Löwenthal [1374,1375]) Some authors however emphasize that the eunuchs fail to develop bushy eyebrows which are seen in many men after the fourth decade.[1376] It is known since antiquity (Aristotle) that eunuchs do not become bald headed like many other men However precocious graying is mentioned [1377]

Late Castration —If the loss of the testicles occurs after puberty the changes *are less pronounced* and even libido and potency may remain to some degree The observations on such cases are plentiful Hot flashes are felt by some castrates shortly after the loss of the testicles but they do not become as distressing a symptom as sometimes occurs in the female climacteric. There is a tendency towards loss of body hair[1378] which usually takes on a female distribution [1379] A patient of Lisser[1364] who shaved four times weekly before the loss of his testicles had to shave only once a week afterwards. In some adult castrates the beard *remained unaffected* [1374,1379]

The skin of the eunuchs is rather thin and remarkably pale with a slightly yellow hue. The *pallor* which is an outstanding characteristic of the eunuch's skin is caused by narrowing of the arterial bed and by a relative lack of melanin resulting from the failure of a colorless promelanin to mature to dark melanin Probably because of this fact there is little or no tanning on exposure to ultra violet light.[1380] Similar phenomena are known in the female (see menstruation) Castrates who work outdoors like some members of the Skoptsy a religious sect in Russia and Rumania which practices castration for religious reasons do not acquire the typical farmer's skin [1376,1381 1382]

The yellow component of the castrate's skin is caused by carotene which is present in excessive quantity [1380] Pallor pigmentation and carotene content can be influenced by testosterone administration The panniculus adiposus is often increased with concentration on the thighs the hips and the abdomen Weight gains of twenty five pounds are common and the basal metabolism is usually lowered [379] Some eunuchs however are lean. Gynecomastia is common[1383] but the breasts consist of fat only and not of glandular tissue [137]

[1374] Löwenthal, K Der Eunuchoidismus des Mannes, Beitr z. path. Anat. u. z. allg. Path 86 436-439 1931

[1375] Scheuer O F Die Behaarung d Menschen, Leipzig, 1933 Curt Kabitzsch.

[1376] Tandler J and Grosz, J Die Skopzen Einfluss der Kastration auf den Organismus, Arch f Entwicklungsmechn d. Organ 30, 2 236-253, 1910

[1377] Marañon, G Manual d las enfermedades endocrinas y del metabolismo, Liberria Hachette, Buenos Aires, 1939

[1378] Hackfield A W Ueber die Kastration bei 40 sexuell Abnormen, Monatschr f. Psychiat Neurol 87, 1-31 1933

[1379] McCullagh E P and Renshaw J F Effects of Castration in Adult Male, J A.M A. 103 1140-1143, 1934

[1380] Edwards, F A Hamilton J B Duntley S A and Hubert G Cutaneous Vascular and Pigmentary Changes in Castrat Men, Endocrinology 28, 119-128, 1941

[1381] Koch, W Die russisch-armenische Kastratensekt der Skopzen Veröffentl a. d Kriegs- Konstitutionspath 2 1-39 1921

[1382] Pittard, E La castration chez l homme Recherches sur les adeptes d une sect d eunuques mystiques, les Skoptzy Arch suisses d anthrop. gén 6 213-230 1932.

[1383] Lange, J Die Folgen der Entmannung (an Hand der Kriegserfahrungen dargestellt) Leipzig Georg Thieme, 1934

The face often has a sleepy expression This is caused by a small fat pad in the upper eyelids which narrows the space between the lids. Slight puffiness of the face is an early and common symptom after adult castration [1333] The face often becomes finely wrinkled in a peculiar shriveled or papyraceous way which does not correspond to the normal facial folds.

Increase of the thickness of the nails in an adult castrate which could be reversed by testicular substance was seen by Lisser [1334] although nail changes were missed in the twelve cases of McCullagh and Renshaw [1317]



Fig 90 — Eunuchoid in young man aged 18 years Beard, axillary chest, pubic hair absent. Fronto-temporal hair line without masculine notch.

All or some of the features of eunuchism may be seen in the syndrome of eunuchoidism which is not rare as the experiences in the military induction centers have shown Heredity is a factor in this constitutional endocrine anomaly [11, 1335]

The *male climacteric* is an objective reality[1336] and not mainly a matter of neurasthenia and hypochondry [1337] However no definite dermadromes which

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[1334] Lisser H Onychauxis in an Eunuchoid Remarkable Improvement by Implantation of Testicular Substance Arch Derma & Syph 10 180-182, 1924

[1335] Carmichael, H T and Kenyon, A T Eunuchoidism, Arch. Neurol & Psychia 40: 717-742, 1938

[1336] Heller C G and Myers, G. B The Male Climacteric J A M A 126 472, 1944

[1337] Rietz, V Das Problem des männlichen Klimakteriums, Wien Klin Wchnschr 49: 1133-1139 1936.

are linked to the physiological decline of the testicular function have become known. The keratoderma palmarum et plantarum climactericum described by Haxthausen in the female has also been reported in ageing men.[illegible] In a recent analysis of 54 cases of the male climacteric,[illegible] itching, hot flashes and sweating occurred in about one third of the instances. Androgenic therapy seems to be promising.

Common Baldness

Since the common type of baldness occurs almost exclusively in men, it is natural to think of causes peculiar to the male sex. R. O. Stein[illegible] who first described the calvities frontalis (see puberty) which is largely characteristic of the male hairline and is usually lacking in eunuchoids and women, has suggested that the common baldness of males is a continuation of the physiological frontal baldness. Seborrhea and tension of the scalp with impaired circulation are contributing factors. Several authors[illegible] suggest that baldness of the common type is a generalized primate trait which occurs in a similar pattern in apes and monkeys. Heredity is a definite factor.[illegible] In 1932 Sabouraud[illegible] quoting the famous observation of Aristotle that neither the child nor the woman nor the castrate become bald added that we know hardly more on the subject. The situation does not seem to have changed. However, we have learned that administration of male hormone to eunuchoids and castrates can produce baldness of the common type. Premature alopecia of the male type has also been seen in virile women with arrhenoblastoma or suprarenal virilism. It ceases to progress when the abnormal masculinization ends.[illegible]

Unfortunately endocrinology has not yet shown a practical way to prevent or cure baldness. Castration prevents baldness but this surgical approach has so far not been suggested in seriousness, though it has been hinted.

Gynecomastia

Gynecomastia may occur in an otherwise normal puberty. Ten cases were recorded per 100 000 personnel in the United States Navy.[illegible] The type occurring in otherwise normal young men is more often unilateral than bilateral.[illegible] It is also occasionally seen in the male climacteric.[illegible] It is often pronounced in Fröhlich's syndrome and in eunuchoidism. In rare instances it is associated with a variety of neoplasms which have retained the endocrine functions of the

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[illegible] Henschen, O. Palmar and Plantar Keratoderma, Schweiz med Wchnschr 70: 660-69, 1940.

[illegible] Werner, A. A. Male Climacteric. 54 Cases, J A M A 127: 705-710, 1945.

[illegible] Stein, R. O. Ueber die Beziehung des Haarwachstums und Haarausfalles zum endokrinen System und über die Möglichkeit einer endokrinen Therapie der Glatze, Wien klin Wchnschr 49: 449-452, 1936.

[illegible] Miller, G. S., Jr. Human Hair and Primate Patterning, Smithsonian Misc Collect 85: 10, 1931.

[illegible] Rattner, H. Ordinary Baldness, Arch Dermat & Syph 44: 201-212, 1941.

[illegible] Osborn, D. Inheritance of Baldness, J Hered 7: 347, 1916.

[illegible] Hamilton, J. B. Male Hormone Substance is Prerequisite and Incitant in Common Baldness, J Invest Dermat 6: 473-474, 1942.

[illegible] Weber, G. F. Gynecomastia in the Navy, Mil Surgeon 95: 376-379, 1944.

[illegible] Menville, J. G. Gynecomastia, Hygeia 21: 187-189, 1943.

[illegible] Richardson, T. A. Gynecomastia, Lancet 1943, 1: 304-305.

soil from which they originated. Such tumors include[illegible] instances of adrenal cortical tumor,[illegible] eosinophil adenoma of the anterior pituitary, pinealeoma, neoplasms of the midbrain or of the hypothalamus and thymic tumors. The best known endocrine neoplasmatic cause, however, are tumors of the testicle, especially teratomas and the rare chorionepitheliomas with high estrogen production.[illegible]



Fig. 191. Fig. 192. Fig. 193.

Figs. 191, 192, 193.—Pseudohermaphroditism. Female aged 19 years. Ovaries, infantile uterus, vagina of 10 cm. length, female distribution of pubic hair but erigible phallus of 4 cm., scrotal appearance of labia majora, male breasts, male body configuration, husky voice, vigorous beard growth. Lives as girl. (Courtesy Wisconsin General Hospital.)

[illegible] Weber, F. P.: Gynecomastia—Endocrine Tumors, M. Press 211: 185-187, 1944.

[illegible] Kries, B.: Ueber Gynäkomastie: ein Beitrag zur Kenntnis der Beziehungen zwischen Keimdrüsen und Geschlechtscharacteren, Arch. Gynäk. 141: 603-635, 1930.

[illegible] Geschickter, C. F.: Suprarenal Tumors, Am. J. Cancer 23: 104-134, 1935.

[illegible] Sterjehann, A. R.: Ein Fall von Chorionepitheliom im Hoden mit Gynäkomastie, Frankfurt. Ztschr. f. Path. 43: 60-93, 1932.

[illegible] Jordans, G. H. W.: Gynäkomastie bei einem Kranken mit malignem Testistera [illegible], Nederl. tijdschr. v. geneesk. 77: [illegible], 1933. [illegible]

[illegible] Zondek, B.: Maligne Hodentumoren und Hypophysenvorderlappenhormone. Hormonale Diagnostik aus Harn, Hydrocelenflüssigkeit und Tumorgewebe, Klin. Wchnschr. 11: 274-279, 1932.

[illegible] Gordon, W. G.: Pathology of 142 Cases of Primary Neoplasms in Man, J. Urol. 43: 722-733, 1940.

[illegible] Lewis, M. L.: Gynecomastia, J. Clin. Endocrinol. 1: 511-514, 1941.

[illegible] Bosse, H. K. and Evans, N.: Chorionepithelioma in Male and Gynecomastia, Am. J. Surg. 58: 128-132, 1942.

This symptom has furthermore been seen to follow prostatectomy and the administration of cholesterol [1407] adrenal cortical extract [1408] and desoxycorticosterone (Doca) [1409] It is a frequent finding in cirrhosis of the liver (see chapter on diseases of the liver) Failure of the cirrhotic liver to destroy estrogens may be the cause of gynecomastia in severe hepatic disease [410] (Zondek B after Edmundson)

Testosterone has been shown to cause complete regression or reduction of the hypertrophy of the male breast in 26 out of 28 cases.[1411] Surgery has been recommended [1396]

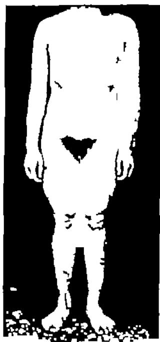


Fig 194 —Same patient shown in Figs. 191 193 (Courtesy Wisconsin General Hospital)

Hermaphroditism

The presence of testicles does not necessarily produce male sexual characteristics Female hair and other sex characteristics have been found together with microscopically verified testicles [412] In a case of hermaphroditismus veru

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[1407] Dunn, C W Stilbestrol—(Estrogen)—Induced Gynecomastia in Male J.A M A 115 2263-2264 1940

[1408] Bronstein, T P Gynecomastia, Endocrinology 24 274-277 1939

[1409] Lawrence, R D Gynaecomastia Produced by Desoxycorticosterone Acetate (Adrenal Preparation) Bri M J 1 12 1943

[410] Glass, S J Edmondson, H T and Soll S. N Sex Hormone Changes Associated With Liver Disease (Gynecomastia in Cirrhosis) Endocrinology 27 749-752, 1940

[1411] Hoffman, W J Gynecomastia, Hormone Therapy Am. J Cancer 36 247 251 1939.

[412] Weisman, A T and Schwartz, A Intersexuality J.A.M A 117 2246-2251 1941.

lateralis[1944] with a testicle in the right side of the scrotum and an ovary and uterus in the left side of the scrotum breasts, pubic hair and other characteristics were of female character [43] They changed to the male after the removal of the ovary and uterus.

Tumors of the Testicles

Except for the symptoms of precocious puberty and gynecomastia which may be caused by tumors of the interstitial tissue of the testicles no skin manifestations seem to be known in tumors of the testicles.

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[43]Lattimer T K Engle, E. T and Yeaw R. C True Hermaphroditism, J Urol. 49 481-498 1943.

CHAPTER XX

DISORDERS OF THE ENDOCRINE GLANDS

THE OVARIES

Our knowledge of the influence of the ovaries on the skin in animals is much greater than that of the comparable facts in man. In the capon it is possible to produce a female plumage by injections of folliculines.[44] The feathers of an adult capon are so sensitive to injections of estrogens and placenta extracts that the failure to inject the hormones one day a week in a series of daily injections is recorded by a black bar in the breast feathers in their regeneration after being plucked.[44] This pigmentary reaction can be used as a pregnancy test[104] utilizing urine which can be read in 48 hours. In the oophorectomized Leghorn chicken the injection of small doses of theelin in olive oil causes a change in the regenerating feathers from male type back to female so that alternating bands of female and male color can be obtained.[47] While the time for the regrowth of the hair after shaving is the same in both sexes in immature rabbits it is shorter in the mature female, longer in the mature female castrate and shorter again in males feminized by estronization.[108] Infiltration of the capon skin with estrogen locally inhibits the characteristic feather changes seen in castrates.[109-110] Continued subcutaneous injections of estradiol benzoate produces shagginess and marked loss of hair in the rat. The estrogen treated rat has a thinner dermis and epidermis and the sebaceous glands are reduced in size and number. All these changes can be prevented by administration of androgen.[70]

The implantation of ovaries into the kidneys of castrated male guinea pigs produces intense pigmentation of the nipples unless these are situated in albinotic skin.[111]

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[1]Caridroit, F. De l'action du benzoate de folliculine sur le plumage du coq domestique. Compt rend Soc d biol 119 523-526, 1935.

[44]Juhn, M, D'Armour, F E and Gustavson, R G. Plumage and Oviduct Response to Female Hormone in Fowls, Endocrinology 14 349-354 1930.

[104]Greenwood, A W and Blyth, J S S. Diagnosis of Equine Pregnancy. Proc Roy Soc London, S B 116 247-257 1934.

[47]Mitchell, J B J. Action of Theelin on the Domestic Fowl, Proc Soc Exper Biol & Med 30 500, 1932.

[108]H C K and Frazier, C N. Effect of Ovary and of Urinary Estrogens on Growth of Hair in Rabbit. Anat Rec 77 155-16, 1940.

[109]Quin, J P and Burrows, W H. Effect of Female Sex Hormone on Plumage Color. J Hered. 26 290-303, 1935.

[110]Greenwood and Blyth. Variation in Plumage Response of Brown Leghorn Capons to Estrone, Proc. Roy Soc London, B 118 97-122, 1935.

[111]Freud, J. On the Biological Tests of the Female Sexual Hormone. Menformon. Influence on Feathers, Rev gen Physiol 67 371 1932.

[70]Bloch, Br and Schraff, A. Experimentelle Untersuchungen über den Einfluss des Ovarial Hormons auf die Pigmentbildung. Arch f Dermat u Syph 165 264-290 1932.

Ovarian Insufficiency

In *aplasia* of the ovaries the pubic and axillary hair is sparse or lacking. The rest of the hair has in some cases been seen to be underdeveloped.[illegible]

In B. Bloch's[illegible] case juvenile cataract and poikiloderma were present.

Primary ovarian insufficiency may lead to a habitus with overlong extremities and also to dwarfism.[illegible] The syndrome of primary ovarian insufficiency is characterized by excessive amounts of urinary follicle stimulating hormone and low levels of 17 ketosteroids. There is lack of breast and uterine development and other symptoms of infantilism. The axillary and pubic hair is scanty but not absent. Albright and his coworkers believe that the growth of the axillary and pubic hair in females is not stimulated by the ovary but by an adrenal cortical hormone (see chapter on Puberty). Melanoderma and mild depressive psychosis in ovarian deficiency have been described by S. Block[187] and later by Bonilla[illegible] and Marañon (after Bonilla[illegible]).

Naturally, a great amount of information is available on the female *castrate*. The cutaneous symptoms after castration of the adult female are essentially those of the menopause. However, it should be emphasized that castration of the woman does not always change her appearance.

Secondary ovarian hypofunction, clinically characterized by amenorrhea or irregularity of the rhythm and amount of the menstrual flow, usually does not cause dermadromes, though hypertrichosis is frequently encountered.[illegible] The hypertrichosis may disappear with the restoration of a normal ovarian function. It seems that hypertrichosis in ovarian hypofunction is due to the relative weakness of the prohibiting effect of the estrogen. Such an imbalance may be caused by ovarian deficiency as well as by adrenal cortical hyperfunction. The urinary excretion of 17 ketosteroids has in many instances of hypertrichosis been found above the normal level.[illegible] Application of estradiol salve and intradermal injections of progynon are able to make the local hair growth disappear,[illegible] but the effect cannot be relied upon. The administration of stilbestrol in primary

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[illegible] Bloch, B. Poikiloderma tropicans mit Mangel der Ovarien ... J. vendler Katarakt. Ueberverreglichkeit ... Parasympathikus, Schweiz med Wchnschr [illegible] 733-736, 1920.

[illegible] Olivet, J. Ueber den angeborenen Mangel beider Eierstöcke. Kastration und Behaarung, Frankfurt Ztschr f Path 29: 477-491, 1923.

[illegible] Geldwasser, J. Ein Fall von Aplasia ovariorum mit pluriglandulärer Dysfunktion und mit durch Transplantation von Ovarien behobener Amenorrhoe. Arch f Gynäk 153: 100, 1933.

[illegible] Varney, R. F., Kenyon, A. T., and Koch, F. C. Ovarian Dwarfism, J Clin. Endocrinol 2: 137-145, 1942.

[187] Block, A. New syndrome, M. Rec 90: 994, 1916.

[illegible] Bonilla, E. Insuffisance ovarienne, mélanodermie et troubles psychiques, Rev franç d'endocrinol 3: 409-426, 1925.

[illegible] Solowjew, Th. Hypertrichose bei Frauen, Arch f Frauenk 13: 153, 1927.

[illegible] Lisser, H. Feminization and Demasculinization of 17 Year-Old Girl by Injection of Stilbestrol, Endocrinology 27: 853, 1940.

[illegible] Strassmann, E. O. Endocrine Treatment of Masculine Hair Growth Associated With Menstrual Disorders in Women, J Internat Coll Surgeons 4: 137-142, 1941.

[illegible] Hamblen, E. C., Cuyler, W. K., and Baptist, M. Urinary Excretion of 17 Ketosteroids in Ovarian Failure in Hirsutism and Virilizing Syndromes, J Clin. Endocrinol. 1: 763-771, 1941.

[illegible] Greene, R. Androgen and Pregnandiol Excretion in Hypertrichosis, Lancet 2: 456-457, 1940.

[illegible] Meade-Fournier, J. C., and Albeaux, A. Absorption of Sex Hormones by Skin. Case of Facial Hypertrichosis Improved by Intradermal Injections of Estrogens, Presse méd. 48: 569-570, 1940.

amenorrhea is often followed by hyperpigmentation of the linea alba and nipples.[illegible] This was not observed in the stilbestrol treatment of menopausal complaints

Ovarian Tumors

Cysts and teratomas rarely cause dermadromes except those connected with hypoovarism Granulosa cell tumors in children may cause precocious puberty[illegible] but there do not seem to be skin manifestations in adult patients.

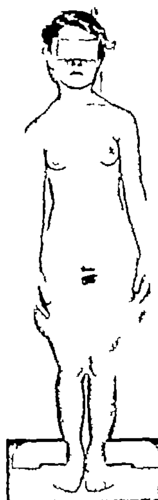


Fig 103 Precocious puberty Female aged 6 years Removal of ovarian t mor at age of 2 years Premature dev lopment started 2 Cervix and [illegible] of adult size Bone age 13½ years. (Courtesy Wisconsin General Hospital

[illegible] Davis, M E Boynton, M W Ferguson, J H and Rothman, H [illegible] on Pigmentation of Endocrine Origin J Endocrinology 8 125, 1945

[illegible] Meyer R Some Species of Ovarian T mors nd Their Relations Sex Characteristics, Am. J Obst & Gynec 22: 697 712, 1931

Dysgerminoma[1494] or seminoma ovarii is rare. This type of neoplasm has been observed in pseudohermaphroditic individuals. The external genitalia are infantile. These tumors, which usually occur in the second and third decades, do not masculinize the patient.[1495]

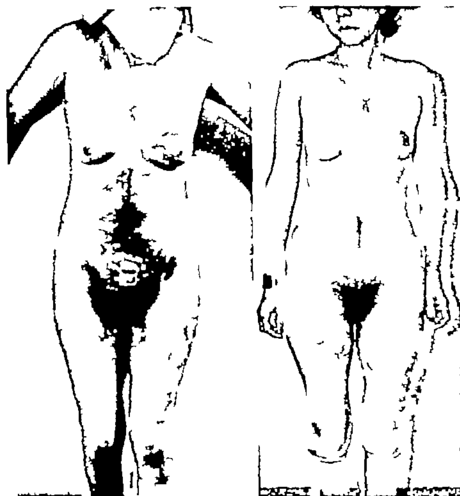


Fig. 96. Masculinizing ovarian tumor before and after operation. (From Blackman, R. L., Am. J. Obst. & Gynec.)

Arrhenoblastomas cause defeminization and masculinization. Baldness of the masculine type may develop; characteristic deposits of fat may vanish; the breast, the other ovary, and the uterus may atrophy, and amenorrhea may ensue. There is enlargement of the clitoris, atrophy of the labia majora, and marked hirsutism of the male type with beard growth. The symptoms are reversible by successful operation. The tumors arise from the seminiferous tubules in the hilus ovarii or from a primitive ovotestis. The histologic picture

shows adenomatous structures resembling seminal tubules and/or epithelial cords. The endocrine testicular function accounts for the deep biological changes.[1436-1441]

In *Carcinoma*[1442] *Luteoma*[1443-1445] *Sarcoma*[1446] and *Hypernephroma*[1447] masculinizing features have been described in rare instances. Kepler[1449] observed



Fig. 197.—Female aged 20 years. Facial hypertrichosis in ovarian tumor of unknown pathology.

Cushing's syndrome in a case of adrenal like tumor of the ovary. There was excessive excretion of 17 ketosteroids but a normal urinary output of estrogens. In rare instances[1448] diffuse erythematous edema of the skin has been observed *as a peculiar form of metastases from ovarian carcinoma (see chapter neoplasms)*

[1437] McIntyre, W. K.: Arrhenoblastoma, J. Obst. & Gynaec. Brit. Emp. 49: 41-50, 1942.
[1438] Sedlis, E.: Geschlechtsumstimmung durch Ovarialtumor (Arrhenoblastoma), Arch. f. Gynäk. 149: 233-236, 1932.
[1439] Mathias, E.: Operativ entferntes Arrhenoblastom mit späterer Schwangerschaft, Zbl. f. Gyn. 57: 449-455, 1933.
[1440] North, E. H.: Arrhenoblastoma, Am. J. Cancer 23: 1-30, 1935.
[1441] Lisser, H., Palmer, A., and Morton, D. G.: Arrhenoblastoma, Removal Followed by Feminization and Pregnancy, Clinics 1: 769-781, 1942.
[1442] Esau: Klimakterische Gesichtsbehaarung, Klin. Wchnschr. 8: 1670-1671, 1929.
[1443] Blackman, R. L.: Tumor With Masculinizing Syndrome, Am. J. Obst. & Gynec. 43: 1036-1041, 1942.
[1444] *Cosacescu, A., Draganescu, S., Georgescu, M., and Dinischiot, G. T.: Lutéinome de l'ovaire contribution anatomo-clinique à l'étude de virilisme ovarien, Presse méd.* 39: 1261-1267, 1931.
[1445] Meyer, J.: Masculinizing Luteoma, Virchow Arch. f. path. Anat. 309: 633-643, 1942.
[1446] Goldberg: Mischgeschwulst des Ovarium (knorpelhaltiges Sarkom) männliche Behaarung, Stimmveränderung und Klitorishypertrophie, Zbl. 53: 1163-1164, 1929.
[1447] Troizkij, V.: Hirsutismus d. Ovarialtumor. Heilung d. Entfernung der Geschwulst, Vrač. Delo 12: 111, 1930; Zbl. 31: 460.
[1448] Urbach, E., Waldow, J., and Casin, C. J.: *Diffuse Cutaneous Metastatic Lesions From an Ovarian Carcinoma*, Arch. Dermat. & Syph. 43: 962-970, 1941.

Small blue *Angiomas Papillomas* and *Fibromas* in large numbers may occasionally accompany tumors of the female sexual organs[1449] Such benign growths of the skin are seen in the menopause as well as in pregnancy and abdominal diseases

Ovarian Relationship of Dermatoses —In the light races women are supposed to be more often brunette than men [illegible] New investigations seem necessary The preponderance of the female sex in some dermatoses is well known Examples are hemangioma lupus erythematosus lupus vulgaris and some other types of skin tuberculosis scleroderma Raynaud s disease chloasma acrodermatitis atrophicans some circumscribed keratoses [illegible] urticaria pityriasis rosea eczema impetigo herpetiformis erythrocyanosis cruris erythema nodosum Paget s disease of the nipple tinea versicolor [illegible]

In order to accept the ovarian etiology in a given dermatosis the claimed relationship should be supported by menstrual or menopausal coincidence disappearance in pregnancy cure by hormonal therapy cure by castration after failure of other therapy and by other evidence of gonadal character The literature of the last fifty years abounds with such reports[illegible] However no dermatosis has been described which by its morphological picture alone would invariably permit the diagnosis of an ovarian dysfunction or disease

Cases of Purpura [illegible] psoriasis, [illegible] keratoderma palmare and plantare [illegible] erythema perstans [illegible] rosacea urticaria and angioneurotic edema

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Men are more subject to the following dermatoses lichen scrofulosorum, lichen planus epidermophytosis inguinalis, Kaposi hemorrhagic pigmentary sarcoma, cancer of the lower lip and mouth, and some others

[illegible] Trevrad, H. W Haut bei sch angeren u. genitalkranken Frauen, Arch f Dermat Syph 47 419 1899

[illegible] Havelock, Ellis Mann und Weib, Würzburg, 1909, Curt Kabitzsch

[illegible] Novak, J Beziehungen zwischen Haut und weiblichem Genitale Biologie und Pathologie des Weibes, vol V 3 Berlin, 1937 Urban & Schwarzenberg

[illegible] Allen, E V The Relationship of Sex to Disease, Ann I Med 7: 1000-1012, 1934

[illegible] Scheuer O. Hautkrankheiten sexuellen Ursprungs bei Frauen, Berlin, 19 1 Urban & Schwarzenberg

[illegible] Rohl Menstruelle Hauterscheinung, Derm Wchnschr 54 541 1912

[illegible] Wiener K Die Beziehungen der Genitalorgane zu Hautveränderungen, Halle 8 1924 Carl Marhold

[illegible] Castillo, C A Sobre púrpura ovárica, Rev med-am d endocrinol 21 767 784 1934

[illegible] Urbach, E Endokrin bedingt jahrzehntelang bestehende Purpura, Zbl 42: 61 1932-1933

[illegible] Schneider G H Ueber konstit [illegible] menstruelle rheumatoide Purpura, Folia haemat. 38 416-421 1929

[illegible] Vogt E Psoriasis bei Ovarialfunktion [illegible], Monatschr f. Geburtsh. u. Gynäk 81 [illegible] 1929

[illegible] Lionetti G Psoriatic Arthropathy in Women Whose Ovaries Have Been Removed Opotherapy [illegible] 48 606-610 [illegible]

[illegible] Bot e-Mira A Su di un caso di cheratodermia simmetrica palmare plantare in donna amenorroica guarita con preparati opoterapici Riv d ostet ginec prat 12 17 1930 Zbl 34 430

[illegible] Mukai T and Shibata, Keratodermia tylodes palmaris progressiva Acta dermatol japon 14 653 66 1929

[illegible] M tunk I and Fajnzeld, A Erythema perstans und das endokrine System, Odess med J 3 649 1925 Zbl 21 302

(see menopause)[1464, 1465] alopecia areata[1466, 1467] eczema[1467-1471] prurigo dermatitis herpetiformis[1472] parapsoriasis,[1473] pruritus[1474] and many other dermatoses have thus been linked to ovarian dysfunction Bohnstedt[1475] found the *urinary excretion of pituitary gonadotropic hormone increased* in rosacea and dermatitis dysmenorrhea symmetrica. Chloasma in nonpregnant women and other pigmentations are in some cases of ovarian origin[1476] They have occasionally been cured by local application of strong estrogen salve[1477]

[1464] Sáinz de Aja, E. A. Urticaria pigmentosa, akutes Quinckesches Oedem und Neurodermitis geheilt d Thyroid- u. Ovarialtherapie, Actas dermo-sif. 22 473-474 1930 Zbl. 36 773

[1465] Black, S Durch endokrine Störungen bedingte Urticaria, Deutsche med. Wchnschr 56: 194-195 1930.

[1466] Říhová, V Alopecia areata und Ovarialstörungen, Česká dermat., Šamberger Festschr pp 830-834 1931 Zbl. 44 423.

[1467] Garnier G Eczema Due to Estrogen-Lutein Disequilibrium 9 Cases, Bull. Soc. franç de dermat. et syph. 46 319-327 1939

[1468] Desaux, A. À propos d la communication de M. Georges Garnier sur l eczéma par l déséquilibre hormonal folliculino-lutéinique, Bull Soc. franç. de dermat. et syph. 46: 627-630 1939.

[1469] Berger M. Dermatologische Beziehungen einzelner Frauenkrankheiten endokrinen Ursprungs, Schweiz med. Wchnschr 65 36-267 1925

[1470] Urbach, E. Endokrin bedingte Haut- Schleimhaut- und Haarerkrankungen, Arch. f Dermat. Syph. 161 493-503 1930.

[1471] Szego, P Ekzem mit Ovarialstörungen, Gyógyászat 68 306, 1928 Zbl. 27 788

[1472] Riecke, E Dermatitis herpetiformis, Handb d. H. u. Gk. 7 2 612, 1931

[1473] Curtis, B. U caso di parapsoriasi lichenoide condizionata guarito con la cura opoterapica, Gior ital. di dermat sif 69: 1423-1437 1928.

[1474] Leszczyński, R von, and Liebhart, S Hormonale Frauendermatosen. I Ueber einige präklimakterische und klimakterische Hautreaktionen, Dermat. Wchnschr 93 1289-1303 1931

[1475] Bohnstedt, R. M. Untersuchungen über Ausscheidung von Prolan A und Follikulin im Harn von Hautkranken, Klin Wchnschr 13 1675-1677 1934.

[1476] Schölzke, K H Chloasma uterinum in nonpregnant women, Med. Welt 13 1413-1414 1939

[1477] Rocca, F Estrogenic Substances in Treatment of Chloasma, J Clin. Endocrinol. 2 317-318 1942.

Chapter XXI

PUBERTY

Puberty is the transition from childhood to adult age seen mainly from the viewpoint of sexual maturing. In the female sexual maturing means the establishment of regular menstruation. In the male emission of semen must be considered the beginning of sexual maturity but this event is much less sharply accentuated and usually forgotten in adult life. Around the beginning of the production of mature gametes is grouped the development of the *secondary sex characters*. Furthermore puberty is a period of intensified organic growth and reorganization which affects almost every part of the body. Finally it is a period of psychic and intellectual ripening and adjustment. The onset of menstruation is but little speeded up by such factors as race and warmer climate, probably more by urban life, better living conditions, and psychological factors.[1477] In the United States the menarche starts between twelve and fifteen years, most frequently at 13.9 (Engelmann after Novak[1478]) compared with 15.5 in the corresponding zone in Europe.

Dermadromes of Puberty.—The establishment of the cycle follows within a year the growth of the pubic and axillary hair. The subcutaneous fat padding gradually smoothens and rounds the skeletal and muscular contours. Typical fat accumulations are found in girls on the cheeks, shoulders, breasts, buttocks, lower abdomen, mons veneris and thighs.[1479] Girls develop less pigment than boys. Neurath [67] considers little bunches of veins in the skin of the thighs to be a female sex characteristic. In boys a palpable, sometimes tender subareolar node of mammary gland tissue often appears at the onset of puberty and disappears at the end. Temporary gynecomastia in boys is seen occasionally.[1480]

The *apocrine glands* start their secretion at puberty, earlier in girls than in boys. These glands represent a type of skin gland which is in close relationship to the gonads. The apocrine glands are sweat glands which develop from the hair follicles and open into the hair follicles, which the ordinary sweat glands, the so-called small or eccrine glands, never do. They do not secrete sweat but give off a secretion consisting of particles of the secreting cell protoplasm. Thus their type of secretion places them between the sebaceous and the sweat glands; many authors consider the apocrine glands to be a rudiment of the scent glands of many mammals. Such glands are known to have a close relationship to the sexual life. The peculiar odor of the human axilla which is different from the

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[1478] Novak, E.: Menstruation and Its Disorders, New York, 1931, D. Appleton & Co.

[67] Neurath, R.: Physiology and Pathology of Puberty, in von Pfaundler-Schlossmann: The Diseases of Children, vol. I, Philadelphia, 1935, J. B. Lippincott Co., pp. 507-[illegible].

[1480] Jung, F. T., and Shafton, A. L.: Mastitis, Mazoplasia, Mastalgia, and Gynecomastia in Normal Adolescent Males, Illinois M. J. 73: 115-120, 1938.

odor of sweat may be due to the chemical characteristics of the apocrine glands which contain iron fat and cholesterol in remarkable amounts [140]

In man the apocrine glands are most densely grouped in a heavy organlike layer in the center of the axillary fossa Less concentrated groups occur in the pubic area particularly in the mons veneris and also around the anus in the areola mammillae (Montgomery s glands) and in the external ear ducts.[141] The thick layer of apocrine glands in the axilla is practically nonexistent in childhood It is more pronounced in the female and much more developed in the Negro than in the white man.[142] It develops early in puberty It is discernible several years before the onset of menstruation [143, 144, 145] Some relationship to menstruation pregnancy and lactation has been claimed [144] but the matter is still controversial. Fox Fordyce disease is a chronic inflammatory condition of the apocrine glands (See Fox Fordyce disease) The axillary concentration of the apocrine glands atrophies slowly in the menopause

The sweat glands especially those of the hands are often remarkably active during puberty

The activity of the *sebaceous glands* is stimulated in puberty This fact together with the keratosis of the follicular opening results in seborrhea and in the formation of comedones and acne Comedones must be considered a physiological development of puberty since they can be found in almost every adolescent

In childhood there are no differences in length abundance diameter and distribution of the *hair* The sexual characteristics of the hair develop during puberty At first there is no noticeable difference in the shape of the escutcheon of the two sexes.

After the seventeenth year the *male* pubic hair extends in a triangle along the midline toward the navel while the female escutcheon has a sharp horizontal upper border line This however is not always the case About one out of eight men has a female distribution of the hair often connected with subnormal beard growth and other feminine stigmata [145] The lack of vigorous pubic hair growth is generally considered a stigma of infantilism The lanugo in the male is coarser often pigmented especially on the chest the arms the legs on the perineum and around the anus *The hairs in the nostrils and ears tend to become coarser in later years* The hairiness in males can reach very embarrassing degrees

The pubic and facial hair in the *female* is probably stimulated by the adrenals rather than by the gonads since the axillary and pubic hair is not completely absent in the primary ovarian failure (ovarian dwarfism) It appears at puberty when the excretion of 17 ketosteroid rises probably due to adrenal cortical activity

[140] Hirsch[illegible] W Anatomie der apokrinen Hautdrüsen des Menschen mit besonderer Berücksichtigung des Achselhöhlenorgans Virchow Arch f path Anat 287 277 [illegible] 1933

[141] Pinkus F Normale Anatomie der Haut Handb d H [illegible] Gk 1 1 1-[illegible] 1927

[142] [illegible] Diagnosis of Apocrine [illegible] and of Fox Fordyce Disease Dermat Wchnschr 107 [illegible] 1938

[143] Kyrle J Histobiologie d Haut Berlin, 1925, Julius Springer

[144] Klaar J Das [illegible] Axillarorgan beim Menschen, Wien klin Wchnschr 39 127 131 1926

[145] Rienk, E Ueber die verschiedenen Arten der männlichen Genitalbehaarung Ztschr f Konstitutionsl 18 164 178 [illegible]

The prepuberty male castrates develop slightly less pubic and axillary hair than normal females Oophorectomized females do not lose their body hair however it falls out in Simmonds disease Addison s disease myxedema and very old age. In all these conditions the excretion of 17 ketosteroids is very low [84] The axillary hair also disappears in hepatic cirrhosis (see cirrhosis)



Fig. 195.—Male distribution, sternal patch of hair N other endocrine abnormalities

Girls of course are supposed to have a smooth skin without noticeable hair except in the pubes and in the armpits. But quite often considerable hair growth along the legs, arms on the upper lip and even in the sternal region of the chest can be seen without any detectable endocrine abnormalities. This tendency is more pronounced in some pigmented races e.g th med terranean [1275, 487] A peculiar accumulation of long pigmented hairs is not infrequently found around the female nipples although it is rarely seen in men

During adolescence the *hairline* which is the border of the scalp hair acquires its characteristic configuration The fairly straight frontotemporal hairline of children develops in boys a more or less marked triangular hairless notch which points in the direction of the vertex where the male baldness will develop later According to R. O Stein [453] who described this calvities frontalis adolescentium it is not observed in castrates nor in eunuchoids nor in women except in masculinizing conditions This rule has not too many exceptions The calvities frontotemporalis is seen in the vast majority of the men and in only less than 6 per cent of the women (Marañon after Mussio Fournier[11])

While the male hair in front of the ears unnoticeably merges into the beard sideburns are seen only in women who ha e other symptoms of hirsutism Marañon (after Mussio Fournier[11]) sees a sexual difference in the hairlines of the nape of the neck In the female the borderline is distinct and shows two lateral prolongations and somet mes a medial one consisting of trong hairs. In the

[487] Friedenthal H Das Haarkleid des Menschen, Jena, 1908
[1453] Stein, R. O Zusammenhaltsmann, Zbl. 18 830 1936

male the transition from the head hair into the lanugo of the nape of the neck is more gradual This characteristic is not very pronounced The male *eye brows* are thicker longer and less regularly implanted They have a greater



Fig 199 —Hypertrichosis of breast The patient is obese, has strong facial hair growth and a decidedly masculine hairline N definit endocrine disturbance could be found. The 17-ketosteroid excretion was normal.



Fig. 200 —Female aged 30 years Calvities emporalis in the same patte as shown in Fig 199

tendency to grow together on the glabella. The development of the eyebrows in the male parallels the general hairiness In middle age some very long hairs appear in the eyebrows. In some men the eyebrows take on a bushy appearance

which is never observed in women The *eyelashes* are stronger longer and more curved in women than in men

Shaving usually becomes necessary between the ages of sixteen and seven teen At first, the rate of *beard* growth is very slow requiring shaving only once a month or less. Marañon (after Mussio Fournier[15]) distinguishes a period of juvenile beard growth on the lateral upper lip zygomatic, chin and submaxillary regions from the mature beard which forms by coalescence of the growth centers.

The color of the hair often deepens during puberty particularly from sixteen to nineteen. This may be due to increased oiliness or to increased pig mentation (Breipohl after Jung [illegible]) The latter is true if there is a hereditary factor of pigmentation which had not yet become manifest. Blond Jewish children often darken considerably in this age.

Certain strands of elastic fibers in the skin of the face which have been described under the name of *elastica mimica* develop at puberty and degenerate



Fig 20 Striae not related to pregnancy ascribed to loss of weight. (Courtesy Division of Dermatology Department of Medicine University of Chicago)

slowly after the age of forty [illegible] *Striae* distensae occur frequently in both sexes during adolescence They are common in the skin of the lower back across the thighs above the pat line and on the upper arms. They usually run transversely to the length of the body or of the limbs in symmetrical rarely unilateral arrangement In the lower back they are typically found in parallel lines below

[illegible] Jung F T The Physiological Changes Incident to Puberty Illinois M J 80 477-484 1941

[illegible] Tehwinkel, K H Ueber die Alterserscheinungen des Hautbindegewebes und über die sogenannte Elastica mimica bei verschiedenen Rassen, Derma Ztschr 63 93-104 1931

the twelfth dorsal vertebra sometimes occupying almost the whole width of the back down to the center of the sacral area. Their[491] appearance often coincides with growing pains in the limbs. The distribution of the striae in puberty suggests a mechanical factor. But it is likely that a toxin which weakens the elastic fibers plays a part. Some authors consider the appearance of striae in infectious diseases an ominous sign but there is little foundation for this belief. (See striae in chapter on pregnancy.)

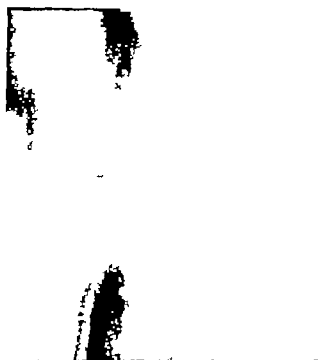


Fig. 203 — Male aged 21 years. Striae of adolescence.

True *precocious puberty* is the phenomenon of early sexual maturity apparently not due to endocrine or cerebral disease but to unknown constitutional possibly hereditary factors. This constitutional type without endocrine tumor occurs in girls and is probably the most frequent variety of precocious sexual development.[492] The advanced development in these cases sometimes starts during intrauterine life. Menstruation without accompanying gross endocrine disease is known to occur several years before the normal time of onset.

All the sequences of puberty are hastened including the changes in skin and hair. The dermatologic aspect of early maturity is discussed in the chapter dealing with adrenal cortical tumors which are frequently respon ble

[491] Petges, G. Vergetures de Croissance ou des adolescents. Nouvelle Pratique Dermatologique vol. VI Paris, 1936, Masson & Cie p. 85.
[492] Novak, E. The Constitutional Type of Female Precocious Puberty. 9 Cases, Am. J. Obst. & Gynec. 47 20-41 1944.

Almost identical syndromes of precocious puberty can be caused by anterior pituitary hyperfunction by pinealomas[449] and other cerebral conditions of heterogeneous etiology[1494] The latter include tumors (glioma) of the corpora mammillaria hypothalamus[1495] and other regions, brain abscesses tuberous sclerosus,[1496] and encephalitis lethargica.[1497] Precocity is also a part of Albright's syndrome (see there) It furthermore occurs in some conditions of the ovaries such as *hyperovarium*[1498] *ovarian cysts*,[1499] *arrhenoblastoma teratoma*[449] *and granulosa* cell tumors. Precocious puberty is a characteristic of hyperorchism caused by neoplasms arising from the endocrinal (interstitial) part of the testis.

Delayed puberty is seen in connection with hypopituitarism hypogonadism and hypothyroidism In gonadal deficiency the thymus is usually persistent.[1500]

Skin Diseases of Puberty

Acne vulgaris is surely the most important and common dermatosis of the puberty age. Pollitzer[1500] in 1914 gave its incidence in the United States as 7.5 per cent of all dermatoses but it seems even more common today There is hardly a boy or girl who is not at some time and in some degree afflicted with it. It is almost a physiological disease

Follicular keratosis, comedo formation and seborrhea are the primary lesions of acne. Inflammation of acute or chronic character with or without abscesses and finally healing with a scar is the sequence of secondary symptoms. The face back and the sternal region are most commonly involved The microscopic examination of early lesions shows a follicular keratosis and epithelial atrophy accompanied by loss of the finer elastic fibrils near the epithelial wall[1501] This latter fact may account for the open pores.

Gonads Age Sex—The most obvious relations exist with the gonads. Acne is extremely rare in early childhood although it has been seen before the age of one year especially in males.[1502-1504] From five to eleven years the incidence curve rises slowly without severe cases. Then it soars distinctly coinciding with the appearance of pubic and axillary hair the development of the breasts

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[449] Bing, J F Globus, J H and Simon, H. Pubertas Praecox. Pinealoma, J Mt Sinai Hosp. [illegible] [illegible], 1938.

[1494] Cuarella, F La pubertà precoce nelle cerebropatie infantili, Rassegna di studi psichiat 24 [illegible], 1935

[1495] Weinberger L. M and Grant, F C Precocious Puberty and Tumors of the Hypothalamus, Arch I Med 67 762 1941

[1496] Corail L and Kisel P Macrogenitosomie précoce Arriération mongoloïde. Adénomes sébacés du visage Rev neurol, 1 [illegible], 1930

[1497] Ford, F R and Guild, H Precocious Puberty Following Measles Encephalomyelitis and Epidemic Encephalitis Relation of Intracranial Tumors and Inflammatory Processes to the Syndrome of Macrogenitosomia Praecox Bull Johns Hopkins Hosp 60 [illegible] 1937

[1498] Zondek Zondek M Fall von vorzeitiger Geschlechtsreife Novy klin arkh. 18 [illegible], 1928 [illegible] 81 [illegible]

[1499] Seguin, H Pubertas praecox als Folge chorionepitheliomatöser Wucherungen, Arch f. Gynäk 150 [illegible]

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[1501] Lynch, F W Acne Vulgaris Histologic Changes in Early Lesions, Arch Dermat & Syph. [illegible] 1940

[1502] [illegible], J J Infantile Acne Vulgaris, J Pediat 20 [illegible] 1942

[1503] Gray A M H Acne in Child Aged 2 Years Proc Roy Soc Med 27 [illegible], [illegible]

[1504] Aitken, B Acne in Infants Brit J Derma 54 [illegible] 1942

and the onset of the menses.[1335] Girls develop acne earlier in life At the age of seventeen almost every boy or girl has some though often inconspicuous blackheads or pimples The severe cases are seen in girls from fourteen to sixteen in boys between sixteen and nineteen [1336] Boys have a little higher morbidity and show severe cases more often This has been shown in investigations of many thousands of adolescents in various countries.[1336-1337]

Some statistics give a lower incidence but it seems that they only take into account the more severely inflammatory cases. After the age of twenty acne becomes less and less frequent but there is no sharp upper age limit Even in the fourth decade acne is not uncommon in men and exacerbations in women at the onset of and even after the menopause occur There does not seem to be acne vulgaris in the aged

Next to the coincidence of acne with the onset of puberty the time relationship to menstruation suggests a gonadal factor It is common knowledge and it has often been confirmed by medical observation that acne exacerbates before during or after the menses the individual case usually remaining constant to type with regard to the time relation of the exacerbation [1338] The intermenstrual remission is often complete. However similar menstrual flare-ups can be seen in lupus erythematosus psoriasis rosacea eczema [1339] and other chronic dermatoses. Therefore the menstrual exacerbation itself is a weak argument for the gonadal cause more so since it occurs in only a certain percentage which varies from about 30 to 75 per cent in several observed series of girls. Menstrual disorders and hypogonadism are no more frequent in girls with acne than in those without acne [1340, 1341, 1344]

A great deal of work with modern methods has been done in order to find better proof of an imbalance of hormones in juvenile acne than is furnished by statistical and clinical methods. This work showed that in patients with acne the output of estrogen in the urine is below the normal level Rosenthal and Kurzrok [1342] and later Rosenthal and Neustaedter [1343] were unable to find any estrin in twenty-seven out of thirty four young women with acne These low urinary estrogen contents in patients with acne were confirmed by a number of authors

In men with acne the excretion of estrogen was also found to be well below normal. On the other hand the output of androgen in men was found to be higher in acne patients while it was found in normal level in women Only Cornbleet and Barnes [1344] found the daily urinary androgen output in male and female

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[1335] Bloch, B Zu Pathogenese der Acne vulgaris, Zbl 44 810

[1336] Illinichsen, J and Ivy A C Incidence in Chicago Region of Acne Vulgaris Arch Dermat & Syph 37 975-993 1935

[1337] Schachtman, J Abnormalities (Adolescence) J Pedia 21 93-103 1942

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[1339] Cohen, E L Incidence of Clinical Acne in Men, Lancet 1 105, 1942

[1340] Bach Ueber die Beziehungen der Acne zu Allgemeinerkrankungen, Diss Bern, 1907

[1341] Cunningham R L and Lansford, C J Acne Related Causes, California & West. Med 35 22 26, 1931

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[1343] Rosenthal T and Neustaedter T Estrogenic Substance in the Blood of Patient With Acne Arch Derma & Syph 32 560-563, 1935

[1344] Cornbleet, T and Barnes, B The Hormones and Acne Vulgaris, Arch. Derma & Syph. 40 219-233, 1939

patients with acne a low normal. Wile[illegible] and his collaborators impressed by the relatively high and unchanging androgen findings believe that the ratio between urinary androgen and estrogen is of great significance They found its value in acne much higher about double of the normal figures. These observations have essentially been confirmed [illegible]

The excretion of sex hormones in the pre-acne age of less than eight is very small and the same for both hormones in both sexes From eight to eleven both steroid sex hormones rise the androgen quicker in the male the estrogen quicker in the female. When adulthood is achieved the normal characteristic ratio of the excreted sex hormones is established [illegible] Acne is characteristic for the years of transition when the ratio is changing just as it is characteristic for the catamenia. At this point of the menstrual cycle the urinary output of estrogens has reached its lowest level [illegible] The androgens excreted by the woman do not fluctuate with the cycle so that a relative preponderance of androgens exists at and around menstrual time when acne is well known to exacerbate There is much evidence that male eunuchoids do not have spontaneous seborrhea and acne [illegible] but may acquire it during treatment with androgenic preparations just as women and also men often do under treatment with testosterone propionate. [illegible] It is noteworthy that acne produced in eunuchoids by injection of testosterone propionate disappeared on withdrawal and reappeared on resumption of the injections.[illegible] Boys generally have an increasing incidence of acne from seventeen to twenty-one years and their cases are often more severe with a greater tendency to pyogenic infection and involvement of the trunk. [illegible] It is a general impression that virile boys are more likely to show acne than those of a more feminine type [illegible] and also that girls with severe acne are of less marked feminity The occurrence of acne in masculinizing tumors of the adrenals the pituitary and the ovaries has often been observed Zimmer [illegible] found gynecomastia more often together with acne than with normal skin but his series is small.

Long before it was possible to prove any changes in the level of sex hormones the attempt had been made to cure acne with organ extracts which in the light of our present knowledge probably had very little potency Later a great number of investigations were made with preparations of undoubted potency Anterior pituitary like gonadotropic hormone prepared from urine of pregnant women has been tried by scores of authors. While most of them found little or no

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[illegible] Lawrence C H and Werthessen, N T Endocrine Dyscrasia of Acne in Women, Endocrinology 27 755-755 1940

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[illegible] Nathanson, J T Towne L E and Aub, J Sex Hormones in Urine and Acne Endocrinology 28 851 1941

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[illegible] Dingemanse E and Laqueur E Nederl tijdschr geneesk, 84 2297 1940

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[illegible] Hamilton, J B Treatment of Sexual Underdevelopment With Synthetic Male Hormone Substance Endocrinology 21 649-654 1937

[illegible] Zimmer E Gynäkomastie und Acne vulgaris, Diss Erlangen, 935

value some claimed benefit.[121] Just as variable were the results with estrogens but it seems that good results outweigh the poor results though not very impressively B Zondek[122] showed that follicular hormones can produce estrus



Fig 203 Abv familial tendency acne F her and son *Below* mother and daughter

phenomena if applied percutaneously This has since been shown in many experiments The practical application of this observation in the treatment of acne by ointments containing estrogens and androgens has mostly been disappointing

[121] Lawrence C H The Anterior Pituitary Hormone A Clinical Study of Its Effects in Acne Vulgaris, J A M A 104 943-957 1935

[122] Zondek B Local Treatment of Acne With Estrogen, Schweiz med Wchnschr 65 1168-1169 1935.

Luteal hormones have been recommended but have had little trial compared with estrogens. The alternating use of large doses of estrogens during the first ten days following the menses and luteal hormone on five consecutive days during the third week of the cycle was followed by lasting improvement in five girls after three months of treatment (Urbach and Schiller[illegible]) Considering the fluctuating course of acne a sceptical attitude toward all reports of small numbers of cases is justified Androgens have been tried in the treatment of acne in spite of the many experiences with their acnegenic effects. The reports are overwhelmingly discouraging In several experimental series [814-1826] controls received injections of bland sesame oil. The effects were about just as good as with androgen in sesame oil—and both were not too poor In summarizing the gonadal relationship of acne one is permitted to say that the age incidence menstrual accentuation occurrence in masculinizing tumors nonoccurrence in male eunuchoids, urinary and blood content of sex hormones and the production of acne with androgen injections proves its existence However the degree of our knowledge of the mechanisms involved has not yet yielded a reliable method of hormonal therapy This opinion is reflected in a symposium on acne of leading American dermatologists Not one out of five dermatologists used hormonal therapy to a larger extent than as an adjuvant.[1827]

Hypertrichosis in girls with or without other signs of endocrine disturbance usually causes a great deal of anxiety The patients or more often the parents soon become worried about the possibility of serious pituitary or adrenal disease. After investigation this question is, fortunately most often answered in the negative But then the cosmetic problem remains. It is beyond the scope of this book to deal with the treatment of hypertrichosis. But it may be mentioned that endocrine therapy so far has only been successful if other endocrine symptoms especially amenorrhea were present.

The *outbreak* at puberty of *chronic dermatoses* like psoriasis lupus erythematosus and epidermolysis bullosa has been observed sufficiently often to make coincidence unlikely [illegible] In Recklinghausen s neurofibromatosis the number of tumors existing from early childhood may suddenly increase so that the fully developed syndrome results. Onset of lipoma formation in puberty has become known in Dercum s disease. It seems correct that in adolescence the tendency to keloid formation is more marked than before A keratosis involving the volar surfaces of the fingers of Japanese girls and mostly starting after the first menstruation has been described by Dohi and Miyake under the name of keratoderma tylodes palmaris progressiva. Takenta[1828] reported 217 cases seen in ten years and Kwabe[1829] 50 cases [1830] Dysmenorrhea and increased basal metabolism have frequently been observed It seems that besides gonadal factors

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[1826] Moffich M Treatment of Acne Vulgaris With Testosterone Propionate Endocrinology 23 603 1938

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[1829] Kwabe M Die sogenannt Keratoderma tylodes palmaris progressiva, Jap J Dermat & Urol 31 21 1932,

[1830] Kitamura, S Keratoderma tylodes palmaris progressiva (Dohi and Miyake) Jap J Dermat & Urol 29 973-1 1929 Zbl, 34 165,

occupational causes play a part. The condition has rarely been seen in boys. The *favorable* influence of puberty is noticeable in certain dermatoses. This is true of urticaria pigmentosa and of infantile eczema Only a small percentage of cases of infantile eczema are carried over into adult age in the form known as atopic dermatitis. Such a stubborn and resistant disease as tinea of the scalp particularly microsporia has a marked tendency to heal spontaneously at puberty although there are exceptions to this rule The fact that tinea of the scalp usually heals at puberty may be due to the higher acidity during puberty The pH of the infantile skin drops from 6.2 — 6 4 to 4.5 — 5 6 [1001]

[1001] Bancroft, J R Hormones and Skin, California & West. Med. 61 60-62, 1944.

Chapter XXII

MENSTRUATION

The Menstrual Cycle[illegible]

The anterior pituitary by means of prolan A a protein like hormone activates the ovary The follicle-stimulating fraction of the prepituitary hormone causes the maturing of the graafian follicle during the first half of the menstrual cycle the luteinizing fraction prolan B after the ovulation on the fourteenth day makes the corpus luteum grow in the empty follicle

During the entire cycle the follicle secretes the steroid estrogens. The estrogen blood level reaches its peak immediately before the onset of the menses and drops to its lowest point during menstruation There is another peak at the time of ovulation at midterm The estrogens cause the proliferative changes in the uterine mucosa during the first two thirds of the cycle. The corpus luteum produces another steroid hormone progesterone which reaches its high in the circulation during the last third of the intermenstruum. It causes the premenstrual secretory changes of the uterine mucosa which are preparatory for the embedding of the ovum. If there is no fertilized ovum forthcoming the uterine mucosa breaks up and menstruation results. The corpus luteum wanes.

More than fifty years ago when menstruation was still believed to be a reflex von Ott [illegible] the first to speak of a menstrual cycle traced over a full month the pulse temperature blood pressure caloric loss muscular power capacity of the lungs and other physiological functions. He found that all these manifestations of vitality increased slowly in intensity during the whole intermenstruum to reach a maximum immediately before the onset of the menstrual flow Then a steep decline during menstruation brings the levels back to the starting point Since these studies many investigations have been made along the same lines. They mostly revealed parallel cyclic changes of vitality and reactivity Many of the cyclic phenomena can be linked with cutaneous changes.

Blood —The number of erythrocytes decreases slightly during the intermenstrual period During menstruation it first rises then falls and rises again after menstruation (Pölzl after Novak [illegible]) The hemoglobin fluctuation is slight. There is a moderate leukocytosis during the first day of menstruation

The *thrombocytes* reach a maximum at the time of ovulation and a minimum during menstruation Catel and Schotola[illegible] traced the decrease of the thrombocytes to the influence of the corpus luteum hormone and suggested the use of the reaction of the thrombocytes as a test for the potency of corpus luteum

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[illegible]Frank, R T Puberty Menstruation, Pregnancy Bull. New York Acad Med 16 83-97 1940.

[illegible]von Ott D Des lois de la périodicité de la fonction physiologique dans l'organisme feminin, N Arch. d'obst et de gynéc 5 803-805, 1890

[illegible]Catel, W and Schotola, H Thrombocyten, Menstruation und Corpus-luteum-Hormon, Med Klin 36 973-976, 1940

preparations The tourniquet test is often positive before[1135] and during men struation[1136 1137 1138] The prothrombin level is probably lowered and the coagula *tion time lengthened shortly before the onset of menstruation* With menstrua tion rise of the prothrombin and return of the coagulation time to normal or even higher than normal takes place

The *blood sugar* shows a premenstrual rise[1144] The carbohydrate tolerance is lowered in menstruating diabetic women and acidosis and coma may be pre-cipitated The more frequent occurrence of acidosis in women below forty five years of age than in males of this age may be linked to the influence of the men strual hyperglycemia[1141,1142]

High blood *cholesterol* has in some cases been seen to return to normal during menstruation[1143] It seems that the blood cholesterol falls during or near menstruation and is followed by a rise above normal level[1144,1145]

There is a tendency to premenstrual *water retention* One third of forty two women showed weight increase before and during the catamenia In some cases edema is noticeable[1146-1148] especially about the lower legs and ankles The urticarial (lymphagogue) reaction to intracutaneous injections of minimal doses of morphine is stronger in the premenstrual period while the vasocon strictive action of adrenalin is weaker at the same time[1149]

The general hydration is probably accompanied by increased succulence of the skin which explains the menstrually increased firmness of the hair im plantation in the skin[1150] On the last premenstrual day it takes more than double the weight necessary to pull a hair out than at the end of the period

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Basler Menstruation nd Haarwurzelfestigkeit Med Klin 25 1111 1113 1929

In the intermenstruum the resistance against pull rises to a medium figure Newer investigations have in part failed to confirm these claims.[illegible]

Menstrual swelling of the *liver* was already observed by Chvostek.[illegible] Menstrual icterus has been the subject of several investigations.[illegible]

Von Leszcynski[illegible] found that in eighty seven out of one hundred menstruating women whom he tested with intracutaneous injections of 0 02 per cent trypan blue the disappearance of the deposit was faster than normal. This test seems to demonstrate an increased activity of the *reticulo-endothelial system*

The sensitivity of the skin to ultraviolet *light* in the premenstrual phase is often higher than normal. The return to normal sensitivity to light occurs during menstruation beginning on the first day [illegible] This may be correlated with the simultaneous fluctuations of the blood calcium potassium and iron[illegible] and especially of the estrogens. In this connection the observations of Hamilton[illegible] concerning the significance of the sex hormones in the tanning of the skin of women may be mentioned. In women who were either in the spontaneous menopause or castrated marked tanning occurred only after injection of estrone or testosterone propionate. Then the pigmentation appeared in areas which as long as two months previously had been exposed to light while areas protected by the shoulder straps and the bathing suit did not tan. Thus the steroid sex hormones acted like a photographic developer

Spontaneous *allergic reactions* like asthma [illegible] as well as those elicited by tests are often stronger immediately before or during the catamenia The sites of old positive intradermal reactions may flare up again during menstruation [illegible] Patch tests are sometimes negative when done in the intermenstruum and positive when repeated during menstruation (Tzanck and Sidi after Urbach[illegible]) Urbach[illegible] advises not to increase the dose for pollen desensitization during the menses because of the possibility of acute reactions. The Dick test for scarlet fever is sometimes temporarily falsely positive during menstruation On the other hand a negative Dick test during menstruation is to be considered highly reliable Some observers[illegible] found the highest reactivity to various allergens on the last

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[illegible] Hansen-Pruss, O C and Raymond, R Skin Reactivity During Menstrual Cycle J Clin Endocrinol 2: 10 [illegible] 1942

day of menstruation the next strongest in the midperiod and the lowest on the premenstrual day Thus the greatest reactivity of the skin would coincide with the period of estrogenic deprivation The sensitivity to tuberculin has been found greatly reduced during menstruation [illegible]

There seems to be little or no influence of menstruation on the results of serologic tests for syphilis.[illegible]

Menotoxin —Popular belief has always held that a menstruating woman exerts a poisonous influence on her environment. Dough kneaded by a menstruating woman would fail to rise and fruit canned in this condition would not keep In 1878 the British Medical Journal discussed the question whether the

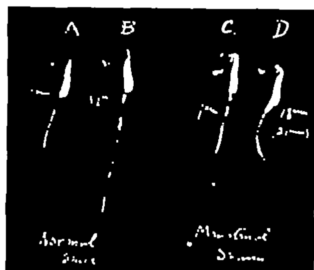


Fig 201 —Toxic influence of menstrual serum on the growth of seedlings of lupinus albus A and C length of roots at the start B root after 24 hours in Shive solution D after 24 hours in 1 per cent menstrual serum in Shive's solution The root has increased only 4 mm instead of 18 mm Normal serum inhibits the growth also but much less. (From Macht D I J Pharmacol & Exper Therap)

general belief was true that if a woman cured hams while menstruating the hams would spoil Similar beliefs are found in almost all countries.[illegible] The question whether cut flowers wither quicker *if handled by a menstruating woman* was first studied seriously by Schlick [illegible] who from his experiments believed that the blood and sweat of menstruating women exert a poisonous influence on cut flowers and yeast He found a marked difference in the life time of cut flowers held over varying periods of time in the bare hands *of menstruating women* compared with that of flowers handled by the same person wearing rubber gloves or in the intermenstrual period Dough kneaded by a menstruating person rose to only half the volume of the control

[illegible] Petersen W F and Milles C Relation of Menstruation to the Permeability of the Skin Capillaries and the Autonomic Tonus of the Skin Vessels, Arch I Med 38 730-735, 1936

[illegible] Ingraham, N R and Meyer V B Menstrual Cycle and the Blood Serologic Test for Syphilis, Am J Syph Gonor & Ven Dis 24 23-29 1940

[illegible] Schlick, B. Das Menstruationsgift, Wien klin Wchnschr 33 395, 1920

On the suggestion of von Gröer, Schick[illegible] called the hypothetic poison menotoxin. Saenger[illegible] in insufficiently reported experiments was unable to confirm Schick's[illegible] claim of a menotoxin. He experimented mainly with mice which after the injection of menstrual blood failed to show toxic symptoms. The most interesting part of Schick's[illegible] experiments which were in accordance with the popular belief was the toxicity of menstrual blood and sweat to plants. Macht[illegible] who had developed a much more sensitive and quantitative phytopharmacological test method confirmed the existence of a menotoxin with well planned and controlled experiments. He together with Lubin[illegible] used the length of roots and stems of growing lupinus seedlings and the cultural growth of yeast as indicators. They found a toxic substance present in the serum, blood cells, saliva, sweat and milk of practically every menstruating woman. With their seedling method it was possible to differentiate between the saliva of menstruating and not menstruating women. The hypothesis of a menotoxin (also toxic to small mammals) was later supported by several investigators[illegible] but the exact chemical nature of the menotoxin or the menotoxins is not known.

As far back as 1923 Patzschke and Sieburg[illegible] had found that the choline content of the sweat of menstruating women was eighty to one hundred times higher than normal, while at the same time in the blood the choline content increased only eight to nine times. These findings, substantially confirmed by Klaus,[illegible] suggest an elective accumulation and excretion of the metabolic toxin in the sweat glands[illegible] or its production in the skin. The high choline concentration in the sweat or in the skin may well be one of the causes of menstrual exanthemas.[illegible] Macht in more recent studies[illegible] suggests that the phenanthrene derivatives cholesterol and oxycholesterol might be menotoxins. The substances are related to the steroid sex hormones. One also has to consider certain highly toxic substances in the menstrual discharge. Such toxins are formed in the endometrium.[illegible] The histamine content of the menstrual blood is much higher (12.5 to 2,000 times) than that of the circulating blood.[illegible] Increased activity of the apocrine sweat glands during menstruation is likely. The gonadal relationship of these glands is known. (See Puberty, Menopause.)

The hairdressers claim that permanent waves are not successfully given during the menses, but this has not been proved.

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day of menstruation the next strongest in the midperiod and the lowest on the premenstrual day Thus the greatest reactivity of the skin would coincide with the period of estrogenic deprivation *The sensitivity to tuberculin has been* found greatly reduced during menstruation [1963]

There seems to be little or no influence of menstruation on the results of serologic tests for syphilis.[1964]

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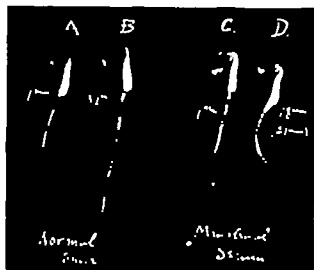


Fig 201 —Toxic influence of menstrual serum on the growth of seedlings of l pinus albus A nd *C length of roots at the start B root after 24 hours in Shive's solution D fter 24 hours in 1 per cen* menstrual serum i Shive solution. The root has increased only 4 mm. instead of 15 mm Normal serum inhibits the growth too but much less From Macht D J J Pharmacol & Exper Therap)

general belief was true that if a woman cured hams while menstruating the *hams would spoil Similar beliefs are found in almost all countries.* [78] The question whether cut flowers wither quicker if handled by a menstruating woman was first studied seriously by Schick [1965] who from his experiments believed that the blood and sweat of menstruating women exert a poisonous influence on cut flowers and yeast He found a marked difference in the life time of cut flowers held over varying periods of time in the bare hands of menstruating women compared with that of flowers handled by the same person wearing rubber gloves or in the intermenstrual period Dough kneaded by a men truating person rose to only half the volume of the control

[1963] Petersen W F and Milles, C Relation of Menstruation to the Permeability of the Skin Capillaries and the Autonomic Tonus of the Skin Vessels, Arch Int Med 38 730-735 1926

[1964] Ingraham, N R and Meyer V R Menstrual Cycle and the Blood Serologic Test for Syphilis, Am. J Syph Gonor & Ven. Dis 24 23-28 1940

[1965] Schick, B Das Menstruationsgift, Wien klin Wchnschr 33 395 1920

the menstrual cycle Successful endocrine therapy is an important argument for the hormonal origin of menstrual dermatoses. The increased knowledge of allergy has done much to explain the menstrual repetitions of some skin lesions. As early as 1907 Wolff Eisner[illegible] suggested the allergic nature of *menstrual urticaria*. The regularly repeated fluctuations of a great number of substances which may have allergenic qualities and the increased reactivity provide an excellent set up for allergic phenomena. It is to the merit of Geber[illegible] to have been the first to demonstrate the allergic character of some menstrual dermatoses. In a case of menstrual urticaria he took serum during the time of menstruation and injected it intravenously into the patient during the intermenstruum. This injection was followed by an outbreak of urticaria while it was not possible to elicit such a reaction with serum taken during the intermenstruum. Menstrual serum from another woman did not work in the patient and the menstrual serum of the patient did not work in another woman. The passive transfer with the method of Prausnitz and Kuestner was accomplished and desensitization by means of systematic injections of the autogenous menstrual allergen during the intermenstruum was found to be effective in a considerable number of cases.

Waldbott saw premenstrual urticaria asthma and sneezing after a severe allergic shock caused by an injection of theelin. This observation is of great theoretical interest but so far the evidence is scant.[illegible] Successful desensitization with ultrafiltrate of menstrual blood has also been reported. Menstrual angioneurotic edema is not rare.

The menstrual dermatoses have a definite tendency to recur in the same place as a fixed eruption. This suggests that unknown factors of the terrain play a part in the pathogenesis. It is sometimes possible to change by local X-ray treatment the reaction of such an area and to prevent the recurrence. Since many women take antipyrine for the relief of menstrual symptoms and since antipyrine is known to cause fixed drug eruptions this possibility has to be considered. It sometimes needs the increased sensitivity of the premenstrual period to produce an antipyrine eruption.[illegible] It is of historical interest that the first fixed antipyrine eruption which was described by Brocq in 1904 occurred in a patient who took antipyrine for painful menstruation. The eruption was at first ascribed to her periods (Abramowitz in discussion to Throne[illegible])

In *menstrual urticaria* the eruptions are sometimes confined to the vulva and the surrounding areas. In the typical cases the picture is the same as in nonmenstrual cases of hives.

Angioneurotic edema mostly of the lips or eyelids also occurs in connection with menstruation. In one of the author's cases the first attack occurred after

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[illegible] Wolff-Eisner: Ueber die Urticaria vom Standpunkte der neuen Erfahrungen über Empfindlichkeit gegenüber körperfremden Eiweisssubstanzen, Derm. [illegible] 164-173, 1907.

[illegible] Geber, H.: Einige Daten zur Pathologie der Urticaria menstruationalis, Dermat. Ztschr. [illegible] 143-150, 1921.

[illegible] Waldbott, G. L. in Disc. to Crisp, L. H.: Allergy to Pancreatic Tissue Extract, J. Allergy [illegible] 154, 1941.

[illegible] [illegible] A., Barnes, Y. and Horowitz, A.: Dermatoses cutanéaes médicamenteuses, Bull. Soc. franç. dermat. et syph. 44: 803-805, 1937.

[illegible] Throne, B.: Exanthema menstruale angioneuroticum, Arch. Dermat. & Syph. 21: 1038, 1930.

a childbirth and recurred menstrually for twelve years. This type of onset after pregnancy has also been observed in other cases.[1146]

Menstrual dermographism is known.

Pruritus vulvae menstrualis is not very rare. It is usually taken as a part of the natural congestion of the vulva during the menses and treatment is seldom requested.

Infections

The menstrual period is accompanied by a lowered resistance to many infections.[1144, 1147, 1148] Many surgeons avoid operations during menstruation because of the increased tendency to inflammatory complications. The self disinfecting power of the skin surface is reduced as shown by Fisher[1149] in systematic investigations with *Bacillus prodigiosus*. The serum of menstruating women shows little or no disinfecting power during the last ten premenstrual days in vitro tests with anthrax bacilli (Drexel and Keller quoted by Geller[1150]). Scarlet fever, diphtheria, tonsillitis and furuncles often start during menstruation. It is known in hospitals that girls admitted because of scarlet fever and diphtheria are usually menstruating.[1151] This general experience was confirmed by a study of hospital nurses. They, too, were often menstruating when they came down with scarlet fever.[1152] Of 119 women in the menarche almost 50 per cent were menstruating when they entered the hospital having erysipelas. The menstrual character of the infection is more obvious if the outbreak coincides with menstruation more than once. Menstrually recurrent erysipelas is often dealt with in the older literature.[1153] Cases with 50 recurrences of erysipelas have become known. Erysipelas at the time of the expected but absent menses in one case eight times in succession has been recorded. Jerusalem's[1153] observation of eight cases of monthly recurrent erysipelas in males has not been repeated. The whole matter of menstrual erysipelas has, during the last twenty five years,[1154] found little interest. Premenstrually recurring paronychia has lately been described.[1155] The author saw a case of hidradenitis axillaris which over years recurred quite regularly with the menstruation. In another case, a furuncle-like deep ulceration of the perineum, which took two weeks to heal, accompanied many periods.

[1146] Halberstaedter [illegible] Disease and Pregnancy [illegible] Marchigiana [illegible] 1912 Abstr Dermat Wchnschr p. 1319 1912

[1147] Sprunt, D. H. The Part Played by Age and the Female Sex Hormones in Resistance to Infection. Endocrinol 25 [illegible] 1939

[1148] Sprunt, D. H., McDearman, S. and Raper, J. Sex Hormones and Infection. J. Exper. Med. 67 159-[illegible] 1938

[1149] Fisher, [illegible] Variations in Self Disinfecting Power of the Skin During the Menstrual Cycle. Proc. Soc. Exper. Biol. & Med. 28 [illegible] 1931

[1150] Geller, F. Infektion und menstrueller Zyklus. München med. Wchnschr. 87 1110 1940.

[1151] Meyer, F. C. Kampfmittel gegen Infektionskrankheiten und Menstruationszyklus. München med. Wchnschr. 87 [illegible] 1940

[1152] Hornters, H., Gebhardt, [illegible] and Nordhausen, W. Kampfmittel gegen Scharlachinfektion und Menstruationszyklus. München med. Wchnschr. 87 [illegible] 1940

[1153] Jerusalem. Beziehungen zwischen Menstruation und Erysipel. Wien. klin. [illegible] 1903

[1154] Diados, N. [illegible] Erysipeloides Menstruelle. Venerol. [illegible] 47 [illegible] 1939 [illegible] 81 74

[1155] Reibold. Paronychie die sich vor den Menses [illegible] München med. Wchnschr. [illegible] 1911

Menstrual *herpes* the infectious nature of which has been established[illegible] is the most common menstrual dermatosis About three out of four cases of genital herpes in the female are due to menstruation (Bergh after Steuer[illegible]) In its appearance menstrual herpes is no different from herpes simplex. After a premonitory burning sensation of a few hours red spots appear which quickly develop into crystalline vesicles. These blisters form one or several small groups. They become pustular after one or two days then they dry up and heal without scars in about one week. The primary blister is quickly destroyed on mucosal surfaces. Here the typical appearance is a whitish or red spot with floating remnants of the blister at the edge. On the skin as well as on the mucosa the blisters may merge to form plaques The local lymphatic nodes are often tender and slightly enlarged Next to the genitals the lips and the chin seem to be the most common sites of the eruption Just as the menstrual acne the menstrual herpes is often seen on the chin. Fournier[14] aptly called this "herpes indiscret" Eruptions on the hands on the thighs or elsewhere are much rarer Unusual and more serious events are menstrual herpes eruptions of the cornea[illegible] and of the oral and pharyngeal mucosae The latter sometimes known as herpetic angina can be accompanied by rather severe constitutional reactions.[illegible] The experimental transmission of menstrual herpes into the rabbit cornea has not only been successfully performed[illegible] but contact infections in man are known[illegible] Menstrual herpes appears most often immediately before menstruation but in some instances during or after menstruation The first attacks have been seen to precede the menarche several times in monthly intervals.[illegible] It may occur at characteristic intervals in pregnancy[illegible] or if actual menstruation is disturbed by disease malformation or aplasia of the internal genitals.[illegible] It may also continue to appea for a short while in the early menopause

Menstrual *acne* is usually a menstrual flare up of chronic acne lesions. Possibly in connection with an increased premenstrual activity of the sebaceous glands. After the catamenia the acne lesions become dormant again Macht[illegible] found the menstrual sera f women suffering from acne generally more toxic to seedlings than such sera from women who did not have acne. The blood of young men with acne rarely exerted a phytotoxic reaction The exacerbation of acne appears in some patients before in others during or after the menstruation often keeping thi time relationsh p rema kably constant[illegible] Some authors claim that the chin i frequently affected by menstrual acne.

[illegible] Lipschütz B Weitere Untersuchungen über die Aetiologie des Zoster I Ueber die Mikroskopie der Impfreaction und des generalisierten Bläschenexanthems nach Impfung mit Zoster Arch f Derm Syph 1[illegible] 1[illegible]-[illegible] 19[illegible]

[illegible] Niedermeyer A Menstruelle Herpesrezidive Zbl f. Gynäk 4[illegible] [illegible], 1935

[illegible] Chavanne F Recurring Herpetic Angina. Oto-rhino-laryng Internat [illegible] [illegible], 1940.

[illegible] Kreibig Recidivierender Herpes simplex menstrualis am 3 od 4. Finger der linken Hand mit erysipelatöser Anschwellung des Handrückens od der Aussenseite des Unterarms Zbl 4[illegible] 7[illegible],

[illegible] Touraine A Renault P and [illegible] Herpes récidivant transmis par un porteur sain de virus, Bull Soc Franç de dermat et syph 4[illegible] [illegible] 1937

[illegible] Bettmann, S Herpes sexualis, Deutsches Arch f klin. Med [illegible] 1[illegible] [illegible]

[illegible] Rinsemann Menstruationsherpes Acta dermat-venereol, 1930 abstr Dermat. Wchnschr 7[illegible] [illegible], 1930

[illegible] Solomons, B Herpes as Type of Vicarious Menstruation Dublin J M Sc. 4 [illegible] 2[illegible], 1921

Hemorrhagic Dermadromes—The hemorrhagic tendency is increased during menstruation and the platelet count is lowered. Menstrual *purpura* of all degrees of severity has been known for a long time The purpuric lesions may be petechiae or larger hemorrhagic spots. They may be universal or restricted to certain areas e.g the lower half of the body[1004] In purpura as in other menstrual rashes there exists a tendency to fixed recurrence. Such fixed purpuric lesions have been seen to recur regularly e.g around the eyes [446] or on the thighs.[1006,1007] *Menstrual purpuric exacerbation is sometimes observed in* conditions which themselves have a hemorrhagic tendency Menstruation then provides an additional hemorrhagic factor Cases which allow such an interpretation include one of menstrual purpura in a girl with mitral stenosis [446] and cases of rheumatic fever [448] Here also belongs the case of a petechial menstrual crop on the lower legs which appeared only while a tapeworm was present in the bowel. After removal of the tapeworm the rash failed to appear but recurred menstrually after the recurrence of the taenia. This happened four times.[1008] The bleeding may occur in any open lesion

Varicose luetic or other ulcers have often been observed to bleed during menstruation This phenomenon about which much has been written in the last century has hardly found attention within the last generation Another type of *menstrual ulcer* improves or heals during the intermenstruum and recurs during menstruation More often than the menstrual ulcer has the related *vicarious or ectopic menstruation* been studied In most of the instances the term was used incorrectly since vicarious menstruation should be called only a discharge of blood from some organ other than the uterus with suppression of the menses (Webster) This type has been called substitutional menstrual hemorrhage while for extragenital bleeding of any form occurring together with the bleeding from the uterus the term additional or complementary menstruation should be applied[1478] This mysterious phenomenon has a history in which early over estimation was followed by complete denial of its existence during the late nineteenth century *But since then so many observations* have been recorded that a reserved but positive attitude has become general It is well illustrated by a statement credited to Lawson Tait who said that 'he does not deny that there is such a thing as vicarious menstruation but he does deny the propriety of examiners asking the commonest cause of epistaxis and receiving the answer of vicarious menstruation with approval '[1009]

The nasal mucosa is the most frequent source of vicarious bleeding This is not surprising since menstrual swelling of certain areas of the mucosa covering

[1004] John Purpura dysmenorrhoica, Zbl 46 291 1933
[1005] Beerman, H A Case for Diagnosis (Cutaneous Vicarious Menstruation? Hysteria?) Arch. Dermat & Syph 33 759-760, 1936.
[1006] Hirschberg, A Ueber die Beziehungen der Menstruation zur H t Zbl f. Gynäk. 48 1966-1967 1924
[1007] Halter Prämenstruell recidivierendes, E m Ekzem nach Salvarsandermatitis, Zbl 48 413 1935
[1008] Winkler F Menstruelle Ekchymosen durch Darmparasiten hervorgerufen. Dermat Wchnschr 64 489 1917
[1009] Condit, W H Compensatory (Vicarious Ectopic) Menstruation Xenomenia, Mammae Devö Am. J Obst. 72 235-251 1916

the lower turbinates and the tuberculum was long ago observed by Fliess,[1479] who found these areas during menstruation invariably swollen hypersensitive and apt to bleed on the slightest touch

While ectopic menstrual bleeding from the gastrointestinal canal the lungs and the mammary glands have been observed relatively often sometimes under alarming circumstances, the skin seems to be a rare source Condit[1469] saw a hematoma of hen's egg size develop from a small nevus on the chest in menstrual intervals after the uterus and the adnexa had been removed. After excision of the nevus hemorrhage in the breast occurred. Other reported sources of vicarious menstruation include old scars endometriomyoma of the umbilicus[1480] the nailbeds, the lips and gums. Bleeding from fistulae, cancerous lesions and hemorrhoids must be interpreted in the same way as the menstrual ulcer[1412,1473]

The menstrual history of these cases often reveals irregularities. Puberty and still more the approaching or beginning menopause seem to predispose. Several cases have been observed after hysterectomy[1478] Since extravasations are among the manifestations of hysteria, it is not surprising that psychopathic individuals are often found among the afflicted For the sake of curiosity a twenty four year-old male sexual psychopath with unusual psychic attachment to his mother may be mentioned[1481] He developed monthly cutaneous extravasations in his right arm pit.

Erythemas

Besides such clinically well-characterized menstrual dermatoses as herpes, urticaria and purpura a great variety of transitory menstrual erythemas have been observed. The simplest form is the noninflammatory erythema of the face which sometimes marks approaching menstruation It seems to be a first step towards rosacea which has a marked gonadal relationship (see Rosacea) Occasionally the congestion may involve the conjunctiva.[64] In some cases rosacea starts as a menstrual erythema in the "blush area" and becomes a stable erythema during the menopause. Some menstrual erythemas have the characteristics of erythema exudativum multiforme with nummular papulo-erythematous lesions on the face neck forearms, and lower legs. Some are more vesicular and some show a small vesicle in the center of the red lesion Typical are the herpes iris forms while gyrate or erythema nodosum like lesions are not extremely rare[1481]

There is a tendency to fixed eruption. More rarely the appearance is vicarious appearing only at the time of the missed menstruation Some of the cases which have been described as menstrual erysipelas probably belong to the erythemas. In some cases tonsillectomy[1482] or staphylococcic vaccine cured menstrual crops of erysipelas-resembling erythemas.

[1479] Fliess Beziehungen zwischen Nase und weiblichen Geschlechtsorganen, Leipzig, 1897

[1480] Esser N Endometriomyoma of the Umbilicus, Arch Path 10 878-886, 1930

[1481] Hadley E E Axillary Menstruation in Male Am J Psychiat. 9 1101 1111, 1930, Zbl. 38 142, 1931

[1482] [illegible], D Fälle von Toxicodermia menstrualis mit erysipeloidartigen Erscheinungen, Magy Orvosi? 8 199-201, 1936 Zbl. 54: 614



Fig. 205.—Menstrual eruption resembling erythema multiforme



Fig. 206. Fixed menstrual eruption of eczematous character receding almost entirely during the intermenstruum

Miscellaneous.—Menstrual *chromidrosis* of which substantiated reports can be found in the older literature[illegible] has not been heard of during the last fifty years. It seems that the discolorations of the sweat either were feigned or caused by staining substances from without and not by excreted indigo as had been suggested. *Bloody sweat* has several times been seen in menstrual attacks. It is a hemorrhagic phenomenon of the same significance as other purpuric symptoms.

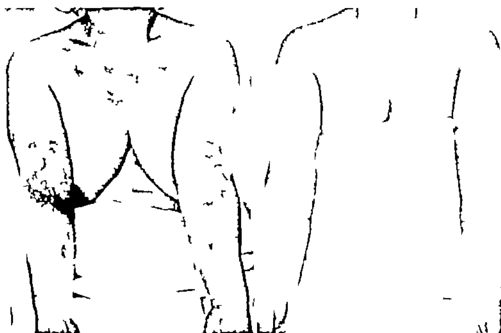


Fig 207 Fig 208.

Fig 207 —Menstrual dermatitis (From Urbach, E Allergy Grune & Stratton, I)
Fig 208 —Same patient in intermenstruum. (From Urbach, E Allergy Grune & Stratton, Inc)

The menstrual darkening of freckles, of the linea alba or of other *pigmentations* is occasionally quite marked The greater pallor of some menstruating women or a rudimentary chromatophoric function of the anterior pituitary may be suggested as an explanation No recent investigations have been published Ruhl's[illegible] observation of menstrual discoloration from gold jewelry has not found much confirmation. Naturally one has to think of silver sulfides developed in more visible amounts by increased menstrual sebaceous secretion Menstrual soreness of the mouth and aphthous ulcerations may become quite troublesome In some cases these eruptions can be prevented by theelin[illegible]

[illegible] Heinemann, M and Andersen, B G Oral Manifestations of Certain Systemic Disorders Yale J Biol & Med 17 583-604 1945

Treatment—In all menstrual eruptions correction of any hormonal disorder should be tried Sometimes the eruption fails to recur if normal menstruation can be restored But this is not always true In some cases menstruation is normal except for the rash but the rash may yet be cured by theelin [1094] Not only theelin but theelin in the first half of the intermenstruum and progesterone in the second half has been given successfully (Urbach[979]) Other hormones or combinations of hormones e.g a placenta preparation and dried adrenal glands [1095] have occasionally helped.

A method of treatment which should be tried in all refractory menstrual eruptions is Geber s desensitization to premenstrual blood[1096] which has been successful in a considerable number of cases. Urbach[976] describes the technique as follows About 20 c.c. of blood is taken at the acme of the premenstrual exacerbation There is some difficulty in determining the right time since much seems to depend on getting the most potent allergen The blood is centrifuged and the serum poured into a rubber capped bottle After 1 10 000 of merthiolate has been added the serum is stored under refrigeration Then 0 2 c.c. of serum is injected intracutaneously every second day The injections are given four successive times into the same site. The site of injection is changed after eight to ten days. Lehner and Rajka (after Urbach[976]) inject 0 4 c.c. daily into two areas in corresponding symmetrical sites While this method was originally used in menstrual urticaria it later proved to be effective in other menstrual dermatoses and complications also e.g in menstrual trigeminal neuralgia.[1096]

[1095] Adrenal Substance in Dermatoses Which May Have Menstrual Factor Arch. Dermat & Syph. 31 865 1935

[1096] Géber H. Desensibilisationsversuche bei Menstruationsintoxikationen, Med Klin. 31 1203-1204, 1935.

Chapter XXIII

PREGNANCY

The fertilized ovum after its implantation into the uterine mucosa causes profound changes in the hormonal balance. Within a few days after the first missed period the anterior pituitary like hormone (chorionic gonadotropin) from the placenta increases in the blood as well as in the urine and reaches a level many times higher than normal after about sixty to ninety days. This peak subsides and remains at a lower but still elevated level until delivery. The estrogen content of the blood and urine increases progressively from the second month until near term. The progesterone level rises until after the fifth month when the corpus luteum undergoes involution. The ratio of the estrogens changes and may assume an abnormal pattern in pre-eclampsia.[1387] With the expulsion of the fetus and placenta a rapid return to the pregravid state ensues with a slump in the normal production of hormones.[1388, 11]

It is natural that the hormonal upheaval of pregnancy is associated with profound changes in the entire endocrine system.

The anterior lobe of the *pituitary* increases to two and one-half times its usual weight and there are characteristic microscopic changes. The large amount of pituitary gonadotropic hormone in the blood and urine is well explained by this hypertrophy. This may account for various stimulations of growth of the skin and its appendages.

After the third month the *thyroid* gland increases in size in almost all cases and its activity is stepped up. Iodine moves from the thyroid into the blood reducing the glandular iodine level about one half. The basal metabolic rate is often raised. If the thyroid is unable to meet the increased demand for thyroxin hypothyroidism may develop. The hyperthyroidism of pregnancy may explain certain sensations of heat, hyperhidrosis and erythema.

The *parathyroid* glands, too, are stimulated probably due to the high demand for calcium for the child's skeleton. The calcium deposits in the mother are drained. The blood calcium level is lowered. Inability to meet the increased requirement may cause a state of hypoparathyroidism with tetany. The ovaries swell and the follicles continue to develop but fail to ripen. The *corpus luteum verum* provides an uninterrupted supply of progesterone needed for implantation, the prevention of uterine contraction and the formation of the decidua. After the first half of the pregnancy the corpus luteum undergoes involution to prepare the termination of pregnancy. Some of its functions are taken over by the pituitary and the placenta. The increased secretion of estrin changes the microscopic picture of the vaginal smears. The epithelial cells increase in size during the first months. Later they become smaller again, so-called oyster-shaped cells appear and leukocytes abound. Just before labor the desquamation of the

[1387] Freed, S. C. Glandular Physiology and Therapy. Chicago, 1941. American Medical Association.

vaginal mucosa almost reaches denudation. The *adrenal* cortex hypertrophies during pregnancy to meet the greater demand. That the demand is greater has been shown by the fact that adrenalectomized cats need more cortical extract for survival during *pregnancy than when nonpregnant*. The lowered glucose tolerance of pregnancy is perhaps caused by a hyperactivity of the adrenal medulla though it has been ascribed to pituitary, pancreatic, liver and renal factors. In the *liver* glycogen disappears from the central portion of the lobules and bile stagnates in the biliary channels.

During the latter part of pregnancy a great amount of nitrogen is stored in the maternal system beyond the need of the fetus. The blood N.P.N. falls. *Albuminuria is common.*

The fat content of the blood increases after the third month giving the blood serum a cloudy appearance. The alkalinity of the blood is increased. Cholesterol is increased in the blood and in the adrenal glands. The blood cholesterol (not the cholesterol esters) increases about 100 per cent.[1054] There is a retention of sodium, potassium, magnesium and sulfur and the excretion of iron and phosphorus is decreased. The retention of most of the minerals *exceeds the needs of the growing fetus.*

Normal Skin Changes.—The skin respond to pregnancy in many ways. According to the *majority of the observers the perspiration* is increased, *especially* towards the end of the pregnancy. Extreme degrees of hyperhidrosis have been seen [[illegible]] in this period. The increase of sweat secretion may take some strain off the kidneys. The urea may rise in the sweat with increasing renal insufficiency. Chlorine increases in the sweat during the first half of the gestation but decreases later. In toxemia it is greatly reduced.[[illegible]] Prolan appears in the sweat of the pregnant women.[[illegible]]

An actual hypertrophy of the sweat glands which had been claimed earlier[[illegible]] [[illegible]] does not seem to have been confirmed in more recent investigations. It has been suggested that the growth of the sweat glands in pregnancy is part of the acromegalic tendencies caused by the pituitary changes.[[illegible]] The *perspiratio insensibilis* decreases with the progress of the gestation but increases during the puerperium. The loss of water through the skin is *particularly low* in toxemia.[[illegible]]

The apocrine gland, the *gonadal* relationship of which has been mentioned in the chapter on Puberty, probably cease to secrete during pregnancy.[[illegible]] The secretion of the *sebaceous* gland increases during the latter half of gestation

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[[illegible]] [illegible] F. Der Lipidstoffwechsel. Zbl. [illegible] 193-212, 1930.

[[illegible]] Pohl, B. [illegible] perhidrosis gravidarum. Zbl. f. Gynäk. [illegible] 1930.

[[illegible]] [illegible] E. The Skin [illegible] of Excretion in the Toxemias of Pregnancy. [illegible] 87: 229-240 [illegible]

[[illegible]] [illegible] Le prolan dans la sueur de la femme enceinte. [illegible]

[[illegible]] Rebaudi. [illegible] in der Schwangerschaft. [illegible]

[[illegible]] [illegible] Ueber die Beziehungen von Hautveränderungen zu den Adnexen der endocrinen Drüsen. Zbl. [illegible]

[[illegible]] Pulvermacher, L. Hautveränderungen bei der Menstruation und in der Gravidität in ihrem Zusammenhange mit der innersekretorischen Tätigkeit der Keimdrüsen. Arch. f. Frauenk. [illegible] 7: 77-79, 1921.

[[illegible]] Seitz, L. Die Schwangerschaftsveränderungen Organe [illegible] ad Drüsen. [illegible] Halban-Seitz, Biologie und Pathologie des Weibes, [illegible] 7. Berlin, 1927. Urban & Schwarzenberg, p. 197.

This seborrhea is especially marked during the last five days[1096] and during labor. Soon after delivery both hyperhidrosis and seborrhea return to normal. It is interesting that the seborrhea of pregnancy is only rarely accompanied by acne.[1097] Usually existing acne is improved. This suggests that not seborrhea but other factors (comedones) are the cause of juvenile acne.

Implantation of particles of normal skin of pregnant women into rats and infantile mice produces the same changes as the pregnant woman's urine. It does not elicit the Allan Doisy reaction. This proves that prolan and not estrogen is the active principle. The prolan is apparently stored in the skin. Skin which has been rendered anemic is not less, and skin with the pigmentation of pregnancy is not more effective than normal skin.[1098]

The epidermal mitoses are more numerous in pregnancy, at least in the guinea pig.[1099] This indicates a stimulated growth which manifests itself in an occasional thickening of the skin, in hypertrichosis and in the development of small neoplasms. The lips may appear thicker, the features coarser and the facial expression may well resemble an early stage of acromegaly.

Pigmentation.—During pregnancy certain areas of the skin which already have a tendency to increased pigmentation receive a stimulus to produce more pigment than in the nonpregnant state. Scars, particularly those from abdominal operation often take part in the pigmentation. Brunettes become much more heavily pigmented than blondes. Generalized melanosis and darkening of larger but circumscribed areas adjoining the well known physiological sites of pigmentation, although a little more common in pregnant hyperthyroid women,[1100] is extremely rare. The linea alba, or more correctly the midline of the abdominal skin, usually becomes pigmented in the third month of pregnancy but sometimes much later, especially in blondes and multiparae.[1101] This linea fusca or *linea nigra* as it is often called, extends from the mons veneris to the navel and, though less often and less pronounced, *into the epigastric region. The line is about one third* of an inch wide and varies in color from light greyish brown to deep brown or black. If it extends to the epigastric area it often forms a one half to one inch wide brown ring around the navel which is called the umbilical areola of Montgomery. The black line is present in 94 per cent of pregnant women. It is occasionally missed in obese women and in very light individuals, rarely in the darker pigmented women. The pull of the ligamentum teres of the liver sometimes causes a deviation to the right of the supraumbilical part, thus *producing a* bayonet-shaped line.

The areolae of the mammillae darken more intensely than the linea nigra, the degree varying again with the color of the hair. There is a certain amount of darkening around the areola proper. This "secondary areola" consists of a network of brownish lines surrounding the lighter follicles. The secondary areola

[1096] Florio, M.: La secrezione sebacea in gravidanza, Arch. di sc. biol. 17: 71-80, 1932.
[1097] Seitz, L.: Schwangerschaftsakne und Haut, Zbl. 273 [illegible], 1933.
[1098] Loewe, A.: Die Haut als Hormonträger in der Schwangerschaft, Zbl. f. Gynäk. 56: 1185, 1932.
[1099] Loeb, L., and Haven, F. L.: The Relation Between States of the Sex Organs in the Female Guinea-pig and the Cell Proliferation in the Epidermis, Anat. Rec. 43: 1-36, 1929.
[1100] Etienne, O.: La pigmentation à type addisonien dans la maladie de Basedow, Rev. franç. d'endocrinol. 6: 190-208, 1933.

though being a sure symptom of pregnancy does not appear before the fifth month [1881]

The hyperpigmentation of the vulva can reach extreme degrees The edges of the labia minora are intensely pigmented The discoloration may



Fig 209 Melanosis of pregnancy Note deviation of pigmented linea alba to the right caused by pull of ligamentum teres hepatis Courtesy Division of Dermatology Department of Medicine, University of Chicago

extend beyond the vulva to the perineum to the inner aspects of the thighs and around the anus Rarely old scars and striae become pigmented The sensitivity to light increases in pregnancy which causes more ready tanning [1887]

The number of noticeable pigmented spots increases in about 25 per cent of the pregnant women Freckles or lentigo-like spots appear or become more pronounced [1888, 1889] An unpigmented mole may become pigmented

[1887] Kehrer E, in Halban, J and Seitz, L Biologie und Pathologie des Weibes, vol 8, Berlin, 1929, Urban & Schwarzenberg, pp 785-789

[1888] Jordan, A Chloasma faciei bei jungen Mädchen, nichtschwangeren Frauen und Männern, Dermat. Wchnschr 96 239-240 1933.

[1889] Goldsmith, W N Pigmentation Brit J Phys Med 11 43-46, 1936

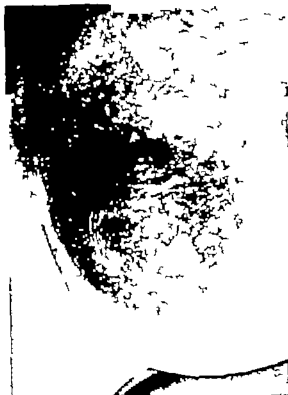


Fig. 310 —Pigmentation of breast in pregnancy



Fig 311 —Chloasma, persisting after pregnancy Irregular menstruation.

"Quae utero gerunt in facie maculam habent." Those who are pregnant have spots on the face. This was known as a fact to Hippocrates but in the nineteenth century[illegible] the connection of *chloasma* with the uterus was still the subject of much controversy. It was either claimed that it had nothing to do with the uterus or that it was identical with tinea versicolor. Chloasma is present in 74 per cent of all pregnant women in the later part of the gestation. Only one third of the cases are marked, the rest are more often pale than pronounced, depending much on the color of the skin and hair. (F. A. Kehrer and Karl Hoffner after E. Kehrer[illegible]) The color may be deepened by exposure to light.[illegible]

The chloasma of pregnancy consists of sharply outlined, often jagged, yellow, brown or grayish spots. They are symmetrical and follow certain patterns.[illegible] They either appear as scattered small spots on the cheeks and nose or as a mask-like discoloration which leaves the lids, the surroundings of the eyes, the pre-auricular areas, parts around the mouth, the temples and almost always a narrow strip along the frontal hairline free. In another type the temples and the zygomatic areas are dark while a trapezoid area in the center of the forehead remains light.[illegible] Transitional types between these patterns occur.

Chloasma usually disappears within a short time after delivery. The first menstruation seems to stimulate the bleaching. Not infrequently the spots fail to vanish for a long time, even for many years. Chloasma has even been seen to persist in the menopause. (Muratori after Sézary and Duruy[illegible])

Chloasma-like pigmentations are not exclusively seen in pregnancy. They have been observed in young girls, nonpregnant women and in men. *Chloasma periorale virginum* is a type of stubborn chloasmatic pigmentation in the lips of young girls.[illegible] The nonpigmented narrow strip separating the chloasma from the vermilion border which originally was described as characteristic in this condition can be seen in many perioral pigmentations, e.g. in perioral vitiligo.

The pigment of pregnancy is melanin. As such it is iron free[illegible] and in its histological characteristics is no different from melanin deposits in other conditions.

The cause of the pigmentations of pregnancy is seen by some authors in the adrenal cortical hypertrophy.[illegible] There is no doubt about the existence of adrenal changes in pregnancy and about the connection of pigmentations with the adrenals, but it has not been proved that just the pigmentations of pregnancy

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[illegible] Kehrer, E.: Schwangerschaftspigmentierung und Chloasma. [illegible] 1934.

[illegible] [illegible], J.: Formen und Ursachen der als Chloasma bezeichneten [illegible] Hyperpigmentationen des Gesichtes. Derm. Ztschr. [illegible] 1930.

[illegible] Sézary, A. and Duruy, A.: Chloasma. Nouvelle pratique dermatologique. [illegible] Paris 1936, Masson & Cie. pp. [illegible]

Wiener, K.: Chloasma periorale virginum. [illegible] 1930.

[illegible] [illegible], F.: Histologic and Histochemical Study of Problems in Pregnancy. Arch. f. Gynäk. [illegible] 1939.

[illegible] [illegible], H. and Schlarberg: Ursache und Bedeutung der Schwangerschaftspigmentationen. Ztschr. f. Geburtsh. u. Gynäk. [illegible] 1935.

[illegible] [illegible]: Les dermatoses, les toxidermies et les inflammations de la grossesse. Gynéc. et Obst. 21: [illegible] 1930.

are caused by the adrenal influence. *It has been shown*[illegible] *that in animals* as well as in man pigmentations identical to those in pregnancy can be produced by the implantation of ovaries or by the injection of large amounts of estrogen under certain conditions. In pregnancy there exists a tremendous increase of the estrogen level The work of Bloch has so far given the best explanation for the pigmentations of pregnancy The pregnancy of one of a pair of siamese twins provided a unique observation The nonpregnant twin developed chloasma as well as the pregnant one. Both chloasmas were concordant. (Hübner after Meirowsky[illegible]) This proves a hormonal or humoral cause of the pigmentation and at the same time the existence of certain local possibly hereditary factors necessary for pigment formation A hereditary factor in chloasma uterinum without pregnancy is established[1379]

It has been suggested that the vitamin C deficiency in pregnancy may have something to do with chloasma. Vitamin C is known to exert an inhibitory influence on melanin formation at least under experimental conditions (see Addison s Disease) However it has not been established that prophylactic administration of Vitamin C in pregnancy prevents or heals chloasma[illegible]

Statistical and tintometric investigations in a large number of pregnant women[illegible] seem to corroborate the belief that heavy pigmentation is associated with an undisturbed pregnancy It is statistically correlated with less vomiting vigorous labor and less danger of atonic hemorrhage and perineal lacerations. On the other hand Grossmann and Schöneberg[illegible] based on laboratory studies deny any metabolic differences between heavily pigmented and nonpigmented pregnant women and attach no diagnostic or prognostic value to this phenomenon

Hypertri hosis.—Occasionally the hair growth of the face and some other areas increases considerably during pregnancy This was already known[illegible] when Halban[illegible] (1906) discovered that hypertrichosis is a physiological phenomenon of pregnancy It is ordinarily so slight that it passes unobserved The light down on the face[illegible] as well as on the arms, legs and the abdomen becomes a little heavier and darker Along the linea nigra it may or may not lead to a

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[illegible] Lipschütz, A Ueber den Ort der Pigmentbildung, Virchows Arch. f path Anat 276 676-680, 1930

[illegible] Bloch, B and Guldberg, O Die Ursache der Schwangerschaftshyperpigmentierung Klin Wchnschr 12: 724-725 1933

[illegible] Bloch, B Erzeugung der Schwangerschafts-Hyperpigmentierung (Chloasma, Linea alba) beim Menschen durch Injektion des Ovarialhormons (Oestroglandol) Zbl 46: 16, 1933.

[illegible] Bloch, B Ueber hormonale Beeinflussung der Pigmentbildung. Zbl 44: 610 1933

[illegible] Forbes, Th R Sex Hormones and Hair Changes in Rats, Endocrinology 30: 465-468, 1942

[illegible] Tschner F Chloasma Gravidarum and Vitamin C Klin Wchnschr 13, II 1614 1934

[illegible] Brunsek H Chloasma gravidarum—Vitamin C München med Wchnschr 84 1236-1237 1937

[illegible] Nishizaki, S Studies on Skin Pigmentation During Pregnancy Jap. J Obst & Gynec. 21 241 243 1938 Zbl 31 63 Jap J Obst & Gynec 15: 865-870, 1939 Zbl 34 [illegible] Jap J Obst. & Gynec 12 374-377 377-390, 1939 Zbl. 35: 236.

[illegible] Slocum A Case of Hirsuties Gestationis, New York M Rec., 1878

[illegible] Hegar A. Zur abnormen Behaarung Beitr z. Geburtsh Gynaek 4 21 1901.

[illegible] Halban, J Ueber ein bisher nicht beobachtetes Schwangerschaftssymptom (Hypertrichosis graviditatis) Wien klin Wchnschr 19: 1906 20: 1907

[illegible] Cedercreutz, A Hypertrichosis superciliaris et in fronte in graviditate aperiens, Acta dermat. venereol. 20: 704, 1939.



Fig. 212 —Hypertrichosis of pregnancy (From Stoddard, F J Am. J Obst. & Gynec 1945)



Fig 213 Same patient shown in Fig 212 4 months after delivery Hypertrichosis which was so marked in pregnancy has completely disappeared. Eyebrows appear less heavy (From Stoddard F J Am J Obst & Gynec 1945)

pronounced male type of hair distribution.[1803] Occasionally a marked hair growth appears just in the midline quite different from the male distribution Halban[1804] showed that two weeks after shaving the abdomen of a pregnant rabbit was covered with thick hair while hardly any growth could be noticed in the controls. It took less than half the time to restore the full hair of a preg nant rabbit than was necessary in the nonpregnant. Similar observations have been made in other domesticated animals. However the increased growth stops before the parturition[1804] The hypertrichosis of pregnancy usually disappears shortly after delivery and sometimes at the time of the first menstruation but it may reappear in subsequent pregnancies. It is suggestive to relate the hypertri chosis of pregnancy to the hypertrophy of the adrenal cortex. Pituitary and thyroid stimulation may play a part.

A pregnancy test based on the sulfur content of the hair compared with that of nonpregnant women has been described by Kosnakoff[1805] It has not found enough confirmation

Alopecia areata has a tendency to disappear in pregnancy but may recur shortly after parturition[1226] In some cases alopecia areata began shortly after pregnancy A seemingly paradoxical and rare phenomenon is the disappearance of hypertrichosis of the upper lip during pregnancy and its recurrence after par turition.[1806]

The daily growth of the *nails* during pregnancy has been found to be in creased from 0 13 to 0 16 mm.[1807]

Striae, Including Those Not Related to Pregnancy—Striae are stripe-shaped lesions which by their form and arrangement across distended skin im mediately show that mechanical tension is a factor in thei pathogenesis. Though by far most common in pregnancy they occur in other conditions in most of which the skin is or has been under mechanical strain caused by enlargement of the volume of tissue which t covers.

Since the striae of pregnan y are the most common example of striation the whole phenomenon may be discussed in this chapter The striae of pregnancy are linear or somewhat wavy stripes of one to fi e inches (2.5 to 13 cm) in length and one quarter to one half of an inch (0 6 to 1 2 cm.) in width. Fresh striae are deep pink or purple the latter color not being due to hemorrhage as one might expect but to the transparency of the thinned skin In the early stage they *look like the marks of whip lashes which in French are called* vergetures. This expression is occasionally used for striae Gradually the thin transparent skin is replaced by a denser scar-like tissue of pearly white color Sometimes old striae are brown with pigment Striae never disappear completely but they may

*Stoddard[1803] found the 17-ketosteroid levels in one of his cases to be 3 3 to 19 mg. in the twenty-four-hour urine compared with the normal pregnancy range of 3 to 6 5 mg

[1803]Stoddard F J Hirsutism in Pregnancy Am J Obst & Gynec 49 417-422, 1945

[1804]Hewel Hypertrichosis in Pregnancy Ztschr f d ges exper Med 104 182, 1938.

[1805]Kosnakoffsky K M Le diagnostic de la grossesse au debut par la réaction chimique des cheveux Gynecologia i Acouscherstvo, p 88, 1934.

[1806]Lombardi S Hypertrichosis an der Oberlippe und ihr Schwinden während der Gravidität, Klin. Wchnschr 13 1037 1038, 1934

[1807]Halban, J and Spitzer M. E. Ueber das gesteigerte Wachstum der Nägel in der Schwangerschaft, Monatschr f Geburtsh. Gynäk. 82: 28-31, 1929.

become quite inconspicous. The surface of fresh striae is smoother than the normal skin sometimes slightly wrinkled transversely or diagonally so that diamond-shaped figures are formed

Fig. 214



Fig. 215

Fig. 214. Striae of pregnancy
Fig. 215. Old [illegible]rophic striae of pregnancy

The palpating finger receives the impression of emptiness and decreased resiliency. This is caused by the lack of the elastic fibers, the skin skeleton. Some striae on the lower abdomen and the sides are raised and more palpable.[illegible]

The striae caused by pregnancy are usually but not always, symmetrical. They are arranged in several groups. One group of longitudinal striae surrounds the navel extending farther downward than upward. A second less pronounced system occupies the lower abdomen; its striae often crossing those mentioned before. A third system runs longitudinally over the hips down to the thighs. A fourth large group forms concentric and approximately circular figures around the sacral area. This group may extend upward as far as the eighth dorsal vertebra. Other mostly smaller bunches may surround the popliteal and elbow areas and cover the shoulders and axillary folds. Their direction is longitudinal. Finally, the breasts show striae arranged in radial fashion around the areola.[illegible] It should be kept in mind that striae are not always caused by pregnancy. This fact is occasionally of some forensic importance. Striae from obesity are mostly found in longitudinal groups on the upper arms, hips, and thighs. Some surround the navel. The striae produced by fast growth during adolescence run transversely. They cross the thighs and to a lesser extent the hips and the lower back. The striae following typhoid fever, dysentery and other infections are most frequently found across the lower thighs just above the knees. Generally striae develop in a direction perpendicular to the maximal tension. If a limb grows longer the striae appear transversely; if it increases in thickness the striae are directed longitudinally. Irregular tractions produce irregular striae, e.g. those one observes occasionally on the side of the chest opposite to a pneumothorax.[illegible]

Striae gravidarum occur in at least 90 per cent of all pregnant women though in very different degree (Credé and many other authors after E. Kehrer[illegible]). These high figures were derived from observations on white European women. Some but not all pigmented races, for instance the women of Java and the negresses of West Africa, are reported to develop striae only very rarely.[illegible] This may be partly due to racial peculiarities or to the massaging of the pregnant abdomen, a custom which has found its advocates in the western world.[illegible] Barfurth claimed that fifteen to thirty minutes of daily gentle kneading of the abdominal skin prevents formation of striae. This treatment is also supposed to bring about a better contraction of the abdomen after delivery. The recommendation does not seem to have been widely followed.

The *histology* of the striae shows that the lesion is situated in the deeper layers of the cutis. There is a marked basophilic reaction and changes in the shape and texture or complete atrophy of the elastic fibers within the striae and an increase in the pathological fibers at the border of the lesion. Here some of them look

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[illegible] Fontana, O. Pregnancy Complications—Atrophic Striae. Ann. di ostet. e ginec. 61: 1243-1254, 1939.

[illegible] Heilmann(?), R. Atrophien der Haut. I. Arzt and Zieler: Die Haut- und Geschlechtskrankheiten, vol. II. Berlin, 1935. Urban & Schwarzenberg, pp. 718-721.

[illegible] Oppenheim, M. Atrophien. Handb. d. H. u. Gk. 8, 2: 800-7 [illegible], 931.

[illegible] Comb[illegible], J. [illegible] cas de vergetures thoraciques unilatérales. Bull. et mém. Soc. méd. d. Hôp. de Paris 43: 006 [illegible]

[illegible] Strata(?), C. H. Ueber Schwangerschaftsstreifen. Ztf. f. Gynäk. 2[illegible]: 431, 1913.

curled as if they had given way to the tension and snapped back. Inflammation has occasionally been noticed in the early stages. Like the blood vessels they are arranged in the direction of the tension. It seems as if the tension does much harm to the elastic and only little to the collagenic fibers. The microscopic findings can be interpreted as evidence of chemical as well as mechanical damage to the elastic fibers. Lately *Fontana*[1661] *has described striae with a marked* inflammatory reaction and lack of distention as expressed by the normal wavy appearance of the papillae.

The microscopic evidence furnishes some support to the opinion of the majority of modern authors that the mechanical *tension* however necessary it may be *is not the only factor* in the pathogenesis of striae. This belief is based on a variety of observations. Some pregnant women develop striae in spite of relatively little tension, others never do no matter how extended their abdomens become. *Of possible significance is the case of a pregnant woman who acquired* striae over the biceps muscle of one arm from carrying books while the same exertion did not cause striation when she was not pregnant.

Tension does not always lead to striae. *There are many cases of enormous* cysts, ascites and edema with extreme stretching of the skin but without striae. While the fat boys with Fröhlich's syndrome rarely show striation, the obese patients with Cushing's syndrome always have them and just in this condition the striae not only are the widest ones one can observe but they are already very *marked when obesity has not reached degrees which could easily* explain cutaneous tears. In men striae are found in 6 per cent.[1662] Men are probably less apt to develop striae than women if one does not consider the striae of pregnancy. The pronounced striation in the basophile adenoma of the anterior pituitary and the pituitary changes in pregnancy suggest a pituitary hormonal *factor.* *Pseudoxanthoma elasticum which is clearly a disease of the elastic* fiber, has been seen appearing in crops during two pregnancies of a patient.[1664]

The loosening effect of pregnancy on the elastic tissue of the pelvic ligaments *which is said to be of pituitary origin may* be caused by *the same agent* which has an affinity to the elastic fibers of the skin. The kyphosis which commonly develops in Cushing's syndrome may also be due to the same elastica loosening *factor* as the striae. In the cases of striae caused by adolescent growth *the actual* tension of the skin is not great compared with other conditions of stretched skin which do not lead to striation. Adolescence is a period of increased pituitary activity. Infection, too, may have a damaging influence on the elastic fibers. Striae are known to occur, though only in a small *minority of the patients,* mostly adolescent, after typhoid fever, dysentery, paratyphoid, in the course of typhus, rheumatic fever, leprosy, syphilis and other infections. Almost always the patients have been bedridden over a long period of time. In these cases the striae are found on the back and often above the patella which may have something to do *with lying in bed with the knees bent.* *In pulmonary tuberculosis*

[1663] [illegible] A. Contribution à l'étude des vergetures linéaires, Ann. d. dermat. et syph. 8: 723-734, 1927.

[1664] Wiener K. Pseudoxanthoma, [illegible] und Gravidität, Zbl 19 3 1925

striae have often been observed on the side of the thorax opposite to the side of the main lesion Increased movement and coughing could explain this localization but this apparently well established fact was not confirmed in twelve cases of striae thoracicae among 5,800 tubercular patients.[1665] Szántó[1666] in his large series always found them on the side of the pulmonary involvement

Transverse striae crossing the spine below the level of the shoulder blades are relatively common in spondylosis deformans but are supposed to be rare in spondylitis.[1667]

Several authors have tried to correlate the color of the hair with the formation of striae. The results are contradictory which probably means that there is no relationship The older primipara is less apt to develop striae than the younger one The same is claimed of the more virile type[1668] and of the short, asthenic megalosplanchnic women [669, 1670] The more striae a woman develops in pregnancy the more likely she is to suffer perineal lacerations but no relation to the labor pains has been established.[1671] It is possible that a hereditary factor has influence on the development of striae. Leven[1672] saw lumbar striae in three of nine siblings and Siemens[1673] twice saw concordant striae in nulliparae who were identical twin sisters. In the unique case of pregnancy of one of siamese twins the nonpregnant one did not develop striae (Hübner after Siemens[1673]) Horneck[1666] observed the appearance of striae after the injection of adrenal cortical extract

The *elasticity* of the skin in normal pregnant women is about one-third lower than normal This lack of elasticity is still more marked in the presence of clinical edema and albuminuria.[187, 1675] It starts in the third month and reaches its peak at the end of pregnancy Though edema may lower the elasticity of the skin it does not increase the tendency to formation of striae

Edema.—A slight increase in the amount of fluid in the skin and in the subcutaneous tissue of the pregnant women must be considered normal. This is to a large extent due to the retaining influence which estrogens and progesterone exert on sodium and water metabolism.[1676] Surgeons know that the cleavability of the tissues is increased during pregnancy The butchers know that it is easier

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[1665] Hammer K Striae Distensae in the Skin of Consumptives, Tubercle 21 349-382, 1931.
[1666] Salnte, O Endokrin bedingte Dermatosen bei Lungentuberkulösen, Zbl 40: 734.
[1667] Sathe, O and Winkler W Striae distensae cutis I Wien. Arch. f inn. Med. 29: 231-252, 1933.
[1668] Beynecke K Schwangerschaftsstreifen und Konstitution, Zbl f. Gynäk. 50 1740-1744, 1926
[1669] Nardelli L Il probabile fattore endocrino nella patogenesi delle "striae cutis" trophicae, Endocrinol patol constit. 1 261 270 1926 Zbl 23 416.
[1670] Nardelli, L La "striae cutis" trophicae Gior ital di derm sif 78 607-637 1926
[1671] Redecart, M Striae gravidarum, Arch. f. Frauenk. 14 190-200, 1924.
[1672] Leven Streifenzeichnung der Regio sacro-lumbalis, Dermat Wchnschr 94 233-236, 1932
[1673] Siemens, H W Die Vererbung in der Aetiologie der Hautkrankheiten, Handb d H Gk. 3 1 168, 1931
[1674] Derio C Alcune ricerche di elastometria cutanea nel campo ostetrico-ginecologico, Ri ital di ginec 11 83 -516 1930 Zbl 80: 210
[1675] Anselm, F Ueber das Verhalten der Hautelastizität während der Schwangerschaft, Diss., 1930, Frankfurt M Zbl 41 202
[1676] Taylor H. C J Warner R C and Welsh, L. A Relationship of Estrogens and Progesterone to Edema of Normal and Toxemic Pregnancy Am. J Obst. & Gynec 45 547-560, 1943.

to skin a pregnant animal than a nonpregnant one. Both observations may be explained by the serous imbibition of the tissues.

While a certain pre-edematous condition is physiological in pregnancy clinically noticeable edema of the legs occurs in 28 per cent of all pregnancies (Hoffner after Scheuer[1682])

McClure and Aldrich s method of testing the skin for impending or not yet palpable edema by measuring the disappearance time of a welt produced by the intracutaneous injection of 0 2 c.c. of 0.8 per cent NaCl solution showed that in pregnancy the disappearance time is almost always shortened [1677] The reduction of the disappearance time is in direct proportion to the degree of edema and can be used as a prognostic sign [1677-1679] The disappearance time is shorter in the legs than in the arms. It is considered to be an unfavorable sign suggesting impending eclampsia if the stasis of a pregnant woman does not disappear on bed rest [1680]

Severe edema of the vulva is a rare complication of pregnancy being encountered three times in 12 000 pregnancies The trouble may repeat itself in subsequent pregnancies The swelling may reach the size of a man s head and may even necessitate cesarean section [1681 1682]

Circulation — During pregnancy the peripheral circulation is marked by *vasomotor instability* Pallor quick changes in the facial color and sensations of heat and cold in the extremities are common particularly in the later months Red or white dermographia is almost always noticeable though varying in intensity [877 1683] This widely held opinion has lately been contested (Piccone after Vignes [1684]) Dermographia is most noticeable on the back the sternal area and on the abdomen above the fundus uteri [11 1685] The reaction is reported to be weaker in heavily pigmented skin

Direct observation of the peripheral blood circulation by *capillaroscopy* has shown that the flow of blood in the capillaries of the lower legs and of the fingernails is often slowed down Segmentation or complete stasis or even regurgitation of the blood from the venules to the arterioles has been observed more often than in controls [1686 [illegible]] It is considered to be an unfavorable prognostic

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[1677]Obladen F Die Quaddelresorption als Frühdiagnosticum der Schwangerschaft Arch f G[illegible] 133 169-172 1928

[1678]Lash A F Intradermal Salt Solution Test [illegible] Normal and Toxemic Pregnancies Surg Gynec & Obst 49 [illegible]-50 1929

[1679]Hornung R Das Verhalten der intracutanen Kochsalzquaddel bei Schwangeren Zbl f Gynäk 61 2723-2730 1937

[1680]Hinselmann H Ueber das Ödem der Schwangeren Zbl f Gynäk 45 1361 1351 1921

[1681]Katzmiller H Elephantiasis vulvae und Schwangerschaft Zbl f Gynäk 61 [illegible] 1936

[1682]Novak L V [illegible] Mary [illegible] 1937 Zbl [illegible] 1937

[1683]Jordan A [illegible] Schwangeren, Zbl [illegible]

[1684]Vignes H Pregnancy complications Evolution of Varieties [illegible] Pregnancy Arch d mal d coeur 22 [illegible]-490 1929

[1685]Piccone L Il dermografismo nella madre [illegible] correlazioni materno-fetali A [illegible] Arch [illegible] 1933

[1686]Hinselmann H Capillarbeobachtungen bei normalen und hydropischen Schwangeren Zbl f Gynäk 45 7 [illegible] 1921

[1687]Hinselmann H [illegible] W und Nettekoven H Beobachtungen und graphische Darstellung der Angiospasmen bei hypertonischen Nierenkranken Schwangeren Zbl f [illegible] k 43 [illegible] 1931

[1688]Hinselmann H und Haupt W Ueber die [illegible] pillarbeobachtung bei Schwangeren, Med Klin 17 270-271 [illegible]

sign if the stases do not completely disappear on changing from the upright to the horizontal position [illegible] In edema and with high sedimentation rates stases are pronounced In hydramnion a tortuous appearance of the capillary loops has been noticed. [illegible] It should be emphasized that stases of course are not a symptom of pregnancy They are the expression of an impaired peripheral circulation and occur in many conditions. The number of capillary loops increases in two-thirds of the pregnant women after the second month but not infrequently only as late as in the seventh or eighth month (Vinigradova after Melbard[illegible])

Two months after delivery the normal number of hair pin type capillary loops is usually found again

The high *permeability* of the capillary wall is shown by the fact that the tourniquet test is positive in 80 per cent of the pregnant women [1897] The serum of blisters produced by cantharides on the skin of pregnant women contains three to four times more lymphocytes than under normal conditions. This observation can be interpreted as evidence of the higher endothelial permeability [illegible] Other studies of cantharides reactions[illegible] showed opposite conclusions.

Pregnancy is by far the most frequent cause of *varicose veins* in women Only about 3 per cent of the women patients of a large varicose vein clinic had their trouble before their first pregnancy [illegible] The incidence figures given by a number of authors vary within wide limits but 50 per cent does not seem too high They most often involve the lower legs only with a preference for the right side. In almost 20 per cent of the pregnant, varicosities of the vulva may produce large bluish tumorlike convolutions.

Hemorrhoids are almost as common as varicose veins of the vulva.

The most simple explanation of the varicosities of pregnancy is the pressure of the uterus on the large pelvic veins. However this cannot be the only cause since varicose veins sometimes develop in an early stage of pregnancy when pressure is negligible They sometimes appear as an early symptom of pregnancy soon after the first missed menstruation (Balard and Mehon after Vignes[illegible]) Even at the common time of appearance in the third month the pressure of the uterus does not give a very plausible explanation since uteri of equal size with tumor hardly cause varicose veins. Other observations[illegible] can be interpreted against the purely mechanical pathogenesis. The varicose veins of pregnancy often appear in crops and the temperature over newly developed varicosities is up to four centigrades higher than over older ones and over the symmetrical skin [illegible] It is interesting that large intra-abdominal tumors may cause edema but rarely varicose veins. The elastic fibers in the wall of the varicose

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[illegible] Fellner M Graviditätsuntersuchungen, Endokrinologie 17 [illegible], [illegible]

[illegible] Melbard S M Valeur diagnostique de la capillaroscopie dans la grossesse et dans le suite puerpérale Gynéc et Obst 37 [illegible], 193[illegible]

[illegible] Spiegler R Cantharidenreaktion und Schwangerschaft, Monatschr f. Geburtsh. Gynäk. 78 47-[illegible], 1929

[illegible] Petersen, W F and Laub, A. F Perméabilité des capillaires cutanées pendant la gestation, Arch Int Med [illegible] 1 1 [illegible]

[illegible] M Dannhof A M Varicose Veins in Pregnancy West J Surg 47 1-44 1939

[illegible] Scheibel, A Varicen und Schwangerschaft Med Klin. [illegible] 1327 1931

The outbreak of the disease is often preceded by premonitory itching without visible changes other than a few wheals. Often in this prodromal period nausea headache and fever may be observed but lack of uniformity characterizes this phase just as much as the later stages. The rash hardly ever breaks out on large surfaces. Usually in one or a few areas e.g around the navel and on some parts of the arms erythematous patches appear which lead to the fully developed syndrome. Wheals prurigo-like small papules vesicles pustules groups of blisters and bullae appear in crops and create a rather polymorphic picture While at times erythematous and urticarial lesions predominate in other periods the abundant bullae may present a pemphigus-like aspect. In some cases aggregated scratched small papules on the trunk and on the extremities resemble prurigo Hebra This dermatosis has been described as a separate dermatosis under the name of prurigo gestationis.[1789] It is probably only a variety of the highly polymorphic herpes gestationis.[1790] Everybody who has observed cases of dermatitis herpetiformis over a long time knows that such prurigo-like stages occur However the separation of prurigo gestationis from herpes gestationis is still stressed by some authors [1644]

The erythematous and vesicular patches of herpes gestationis often spread centrifugally leaving annular or gyrate lesions with accentuated edges and red scaly or pigmented centers. There is little tendency to involve the mucosae Ulceration does not occur and no scars develop unless severe pyogenic infection complicates the course Besides the discomfort of large oozing surfaces in some cases the main complaint of the patients is the furious itching burning stinging or pain which accompanies the crops The attacks of pruritus in particular which can be provoked by various causes especially psychic excitement can make the condition of the gravid woman a most miserable one. It needs all the efforts of dermatological and psychological treatment and in particular the assurance of complete recovery without disfigurement to keep up the morale of the patient

The eruption affects the extremities more often than other regions but no part of the body surface is sure to remain free The nailbeds may become infected and the nails may be shed The outstanding histological feature is the eosinophilia in the blister serum and in the tissue particularly in perivascular infiltrations. Blood eosinophilia is common too Eosinophilia especially in the tissue though not being specific, frequently accompanies allergic diseases and therefore suggests an allergic nature of the dermatosis [11] The recession of the blood eosinophilia is considered a favorable prognostic sign [1791]

The relationship to pregnancy is of course an outstanding characteristic of the disease. Though occasionally an early symptom of pregnancy herpes gestationis has been seen to appear most often in the second half of pregnancy [1790] If there are attacks in subsequent pregnancies the onset may be earlier each time

[1789] Besnier J Sur la question d prurigo, 3rd I ternat. Congr of Derma London, 1 96.
[1790] Bieck E Herpes gestationis, II sdb d II Ok 7 3 637-651 1931
[1791] Eliascheff O Sur la valeur de l éosinophilie dans les dermatoses bulleuses et spécialement dans la dermatite herpétiforme de Duhring Sang 2: 1-3 1925

and the disease may become more severe [1703,1705-1707] Besides this most common type other relations to gestation occur Some pregnancies may remain free and only in a later pregnancy will the first eruption occur (Puente Gross in discussion to Rostenberg[1708]) A normal pregnancy may be had between pregnancies with herpes gestationis.[1709] The onset may be very late, in the last days of pregnancy[1708] or even in the puerperium. The disease may break out during pregnancy improve or heal with the approaching delivery and then be followed by a severe crop during the puerperium.[1710] Characteristically herpes gestationis does not remain after pregnancy as an ordinary dermatitis herpetiformis. In a few cases menstrual recurrencies have been observed. [1711,1712] So far unique is the case of herpes gestationis caused by choriocarcinoma two years after a pregnancy with hydatidiform mole.[1713]

The prognosis is favorable for the mother A fatal outcome is rare and may be caused by sepsis rather than by the dermatosis itself (Schönfeld after Riecke[1703,1705,1714,1715])

The prognosis for the child is unfavorable. Stillbirth ends about fifty per cent of the pregnancies complicated by herpes gestationis. [1707] Babies born alive died in several instances from infection during the first year [1708,1709] Skin lesions in the living or dead child possibly pertaining to the dermatosis of the mother have been reported[1708,1709,1711] but the evidence of true connatal herpes gestationis is not convincing [1708]

The etiology and pathogenesis of herpes gestationis is not much better understood than that of dermatitis herpetiformis. It is just the connection with pregnancy which suggests some explanation Toxemia of pregnancy with damage to the liver to the kidneys and to the skin has often been accused The nitrogen content of the urine is reduced during the eruption and increases with recovery Just as in dermatitis herpetiformis, eruptions may be precipitated by internal or percutaneous application of potassium iodide (Jadassohn's test) However this phenomenon is not constant Endocrine secretions may as in the case of impetigo herpetiformis provide a better explanation than those given today Rostenberg [1708] in his case found the anterior pituitary like principle increased in the urine twenty-six days after delivery In Elliott's[1713] case of herpes gestationis caused by choriocarcinoma the pregnancy tests were strongly

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[1705] Hackert E Ein Fall von Herpes gestationis mit tödlichem Verlauf, Geneesk. Tijdschr. Nederl Indie 69: 1094-1095, 1929 Zbl. 31 67

[1706] Howard, R Herpes Gestationis, Arch Dermat & Syph 26 782, 1932.

[1707] Madden, J F Herpes gestationis, Arch. Dermat & Syph 32 450 1935

[1708] Rostenberg, A Herpes gestationis, Arch. Dermat & Syph. 30 730 1934.

[1709] Rechl, E Contributo allo studio dell herpes gestationis, Gior ital. di dermat. sif. 73 1353-1372, 1932

[1710] Tarot J J and Bouligdoff, H Polymorphe Schwangerschaftsdermatitis, Rev argent. dermat sif 16 1 1932 Zbl 42: 478

[1711] Tommasi, L Contributo alla conoscenza dell herpes gestationis, Gior ital d. mal ven. 65 840-852, 192

[1712] Cruseli A Herpes gestationis dermatite polimorfa dolorosa (Duhring-Brocq) Gior ital. di dermat sif 73 163-174, 1932 Zbl 42 83

[1713] Elliott J A Bullous Dermatoses of Toxic Origin. Case Involving an Association With Choriocarcinoma, Arch Dermat & Syph 37 219-233 193

[1714] Sebastian W Ein Fall von Herpes gestationis, Jap J Dermat. & Urol. 33: 43, 1933 Zbl 45 201

[1715] Gellhorn, G Eczema in Pregnancy Am J Obst & Gynec, 28 409 1933

positive The relationship of *dermatitis herpetiformis* to ovarian function however inconstant and contradictory it may be cannot be easily dismissed in view of the considerable case literature.[1 m] However there still is no satisfactory endocrine *explanation* Some evidence points to allergy The repeated occurrence in pregnancies with each subsequent attack starting earlier and taking a more severe course has its parallel in acquired allergy The urticarial element in the eruption and the marked eosinophilia in the blood blisters and tissues lend support to an allergic hypothesis. Passive transfer has not been successful [171] *A hormone may well act as an allergen Tommasi*[171] *suggests the corpus luteum* such autogenous allergies are known Infection as a cause can neither be denied nor as yet be proved Thus the pathogenesis of herpes gestationis as well as that of dermatitis herpetiformis remains unknown

Based on the hypothesis that herpes gestationis is caused by toxemia and the inability to produce neutralizing antibodies Mayer and Linser[1714] inaugurated the treatment of herpes gestationis with intravenous injections of 10 to 20 c.c. of fresh serum of normal pregnant women With this method Seitz cured 37 out of 38 cases of the various dermatoses of pregnancy This method is still widely applied In some countries this serum is available in ampoules. The serum of pregnant mares has been successfully used too In spite of successes the theoretical foundation of the treatment with normal pregnant women s serum however has become untenable because of the equally successful treatment with normal serum horse serum and especially with Ringer s solution Riecke[1166] gives the following formula for this mixture

Sodium chloride	1 8
Calcium chloride	0 048
Potassium chloride	0 084
Sodium bicarbonat	0 06
Aq distill. ad	200 0

This solution is injected intramuscularly or subcutaneou ly in doses of 150 to 200 c c Sim lar success has been achieved with serum or blood from the umbilical cord with the patient s own blood [71] and with milk. In the published cases one or the other of the above mentioned meth ods especially the normal pregnant w men s serum ha helped One may surely assume howe er that failures of the therapy ha e not been reported with the same zeal as the successes Only a few f the bservers ha e seen a considerable number f cases of thi rare disease and the often irregular course f the dermat sis should be remembered in e aluat ng any method of treatment Lately contradictory reports on the sul fon mides ha e appeared Ovarian extract [71] corpus luteum [709] and vi st n l [71] ha e als been ad ocated

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I yer A and Linser Ein Versuch Schwangerschaftstoxikosen durch Einspritzung von Schwangerschaftsserum zu heilen. Munchen med Wchnschr 57 2737 3739 1910

[71]Watrin, J Dermat it polymorphe douloureuse et stolo/hoothérapie Bull. Soc franç de derma et syph 21 t 1926

[72]Turner J and Zakon J Herpes Gesta ionis, Am J Obst & Gynec 41 825-837 1941

[73]Lewis M Herpes Gest ionis Successful Trea ment W h Sulfathiazole, Arch Derma & Syph 49 1 1943

Purpura.—It has already been mentioned that pregnancy increases the permeability of the capillary wall and that the tourniquet test (Rumpel Leede phenomenon) is often positive. Spontaneous petechiae are occasionally seen under the strain of labor More severe purpuric rashes have been observed [729] some of them with dangerous hemorrhagic complications. They are generally considered toxic. They disappear after delivery[1729] but sometimes recur in subsequent pregnancies, in some cases in the same spot as a fixed eruption [1730] Rushmore[1731] has collected forty-seven cases, mostly of severe purpura in pregnancy The mortality of the mothers as well as of the children exceeded fifty per cent. Some cases have the character of thrombocytopenic purpura. [732] Pregnancy may activate dormant thrombocytopenic purpura or cause the first manifestations of the disease. Besides purpuric skin lesions of great variety in size severe even fatal hemorrhages from the nose, the gums and other sites may occur If treatment fails, termination of the pregnancy is indicated. Bruise like hemorrhagic discolorations of the abdominal wall in and about the umbilicus occur in ruptured extrauterine pregnancy and other intra-abdominal hemorrhages. This is known as Cullen s sign [734]

Miscellaneou Eruptions.—It would be monotonous to describe all the rashes which have been observed in pregnancy other than the well characterized dermatoses. There are morbilliform erythemas, sometimes with eczema or with pruriginous papules. Erythema exudativum multiforme[1735,1736] is also on record. Its differentiation from herpes gestationis is difficult in some cases. Urticaria of pregnancy angioneurotic edema and lichen urticatus are known. Pruritus of pregnancy is common and sometimes of a severity which may cause abortion [1449] Eczema [1469] lichenoid multiple lesions resembling localized prurigo [737] pemphigus vulgaris,[1738] scleroderma[1739,1740] cutaneous atrophy in spots (Temesvary and Oppenheim after Novak[1481]) and other conditions have occasionally been seen during pregnancy sometimes repeatedly and usually healing after delivery Selitzky[1741] described toxic symmetrical dermatitis. It has been said that the pregnant woman has a marked tendency to develop drug eruptions.[1731] Pruritus vulvae and vulvitis of pregnancy is often caused by monilia but is rare compared with

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[1729] Kaiser K. Seltene Hautveränderungen bei Schwangeren, Med. Klin. 34 633-634, 1938.
[1730] Vignes, H and Stiassnie Purpura récidivant au cours de trois gestations successives, Progrès méd 60: 167 168, 1931 Ibid. 1 448.
[1731] Rushmore, S. Purpura Complicating Pregnancy Am. J Obst. & Gynec. 10 553 560, 1925
[1732] Batizfalvy J Pregnancy Complications—Thrombopenic Purpura, Ztschr f. Geburtsh. Gynäk. 118 63-83, 1939.
[1734] Cullen, T S Bluish Umbilicus as Diagnostic Sign in Ruptured Extrauterine Pregnancy Contributions to Medical and Biological Research, etc., New York, 1919 Paul B. Hoeber pp. 420-421
[1735] Green, P Erythema multiforme gestationis, Arch. Dermat. & Syph. 23: 567 1931
[1736] Ebert Toxic Eruption of Pregnancy Multiform Erythema Type, Arch Dermat. & Syph. 16: 509-510, 1927
[1737] Da Lee, J H T Prurigo Annularis, Brit. J Dermat 53: 142-143, 1941
[1738] Klopstock Pemphigus vulgaris Associated With Pregnancy Dermat. Wchnschr 99: 906, 1934.
[1739] Amerbaine K. J and Hofmann, F Ueber Sklerodermie und Schwangerschaft, Ztschr f. Geburtsh Gynäk 103: 60-66, 1932
[1740] Gerard Cas de sclérodermie en bandes à la suite d'une grossesse Troubles ovariens, Le Scalpel 83 812, 939 Ibid 82: 78
[1741] Rosenfeld R Skin During Pregnancy and Puerperium, Urol & Cutan. Rev 48 80-83, 1944

the frequent occurrence of yeasts in the vagina of pregnant women[1722] The typical monilia vulvitis causes itching and redness of the introitus and of the vagina Yellow specks of thrush which are not easily removed without bleeding contain the mycelia. Vaginal thrush caused by *Monilia albicans* was found in 25 per cent of 200 consecutive pregnancies having leukorrhea in Edinburgh Scotland[1723] It is advisable to look for vaginal thrush in order to safeguard the baby from infection at birth Very little is known about the cause of the more severe ulcerations of the external genitalia in pregnancy which have occasionally been seen

Stimulation of Growth —Symmetrical *erythema of the palms* mainly on the thenar hypothenar and finger tip eminences has been described in connection with a variety of internal conditions, notable among them being cirrhosis of the liver and pregnancy The erythema usually leaves the triangle-shaped center of the palms pale The condition is often associated with multiple sometimes pulsating spider like *telangiectases*[1724-1726] The erythema as well as the telangiectases often vanishes after parturition In some cases the spiders result in actual hemangio-endotheliomas which may even become locally malignant and infiltrating[1727]

Preexisting and apparently stationary hemangiomas may start to grow during pregnancy[1723]

Fibroma molluscum gravidarum[729, 1730] is an eruption of small soft pedunculated or sessile sometimes pigmented fibromas which appears in crops during the latter half of pregnancy and disappear after childbirth The little growths appear especially around the neck and in other areas where skin rubs against skin e g under pendulous breasts and in the axillary folds. They may be associated with large brown spots so that a close resemblance with Von Recklinghausen s disease results including the microscopic anatomy The lesions which appear during pregnancy usually[7] but not always[732] disappear after delivery While the widespread or even universal types of fibromatosis gravidarum as it should be called[733] are rare a crop of some cutaneous tags[734] around the neck is common in pregnancy Pregnancy stimulates the growth of skin cancer

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[1722] W[illegible] K. O and Cartwright E W Significance of Vulvovaginitis in Pregnancy J A M A 113 20-21 1939

[1723] Lister W C and Cruickshank, L G On Thrush Special Reference to Vaginal Thrush Edinburgh M J 47 360 1 40

[1724] Konrad E Essentielle Teleangiektasien bei Gravidität Zbl [illegible] 1935

[1725] Walsh E N and Becker S W Erythema palmare and Nevi Aranei Telangiectases, Arch Dermat & Syph 44 616 19 1

[1726] Urbach E Essentielle Teleangiektasien Zbl [illegible] 1939

[1727] Davis [illegible] Cutaneous Hemangio-endotheliomas in Pregnancy J Obst & Gynaec Brit Emp 48 667-673 1 1

[1728] Urbach E [illegible] Zbl 23 1 1930

[1729] Brickner M Fibroma Molluscum Gravidarum Am J Obst & Gynec 53 191 198, 1906

[1730] Brickner [illegible] Molluscum Fibrosum Gravidarum Am J Dermat & Genito-Urin Dis 10 380 1

[1731] [illegible] F Ueber das Fibroma molluscum gravidarum Zbl f Gynäk 61 737 739 1939

[1732] Ward F Multiple Fibromata et Warts in Pregnancy Brit J Dermat 25 142 1913

[1733] Fischl F Ueber den Einfluss der Schwangerschaft [illegible] Wachstum [illegible] Gesch [illegible] Wien med Wchnschr 83 645-64 1933

[1734] Templeton H J Cutaneous Tags of the Neck Arch Dermat & Syph 33 95 1936

produced in rabbits by the application of carcinogenic tar fractions.[1749] The growth stimulating effect of the estrogens is suggested as a cause. The hyper cholesteremia of pregnancy makes one expect a rather frequent occurrence of

Fig. 216.





Fig. 217

Fig. 216.—Fibroma of pregnancy.

Fig. 217. Fibromas (skin tags) of pregnancy. These little tumors may appear early in pregnancy and some may reach larger size.

lipoidoses. It is surprising that xanthoma and xanthelasma in connection with pregnancy is rare (author's case; see also Schaaf[1815]). Growth stimulation may also be the cause of the so-called gingivitis hypertrophica of pregnancy. This

[1749] Krotkina, N.: Ueber den Einfluss von Gravidität und Lactation auf die durch Teerpinselungen erzeugten Epithelwucherungen am Kaninchenohr. Ztschr. f. Krebsforsch. 31: 430-442, 1931.

disorder[1740,1741] frequently starts in the third month In the early stages the gums are red and bleed easily Then they swell especially at the margin The bulging edge may develop folds which cover the teeth and cause considerable trouble. If this hypertrophic stage is restricted to a small area an epulis-like nodule may result. The term epulis gravidarum which has been used is misleading because of the different character of the two conditions. However true epulis occasionally starts in pregnancy and the growth of a preexisting epulis (Seitz) or giant cell sarcoma[1747] may be stimulated The swelling of the gums disappears quickly after delivery sometimes within a week. Gingivitis hypertrophica of some degree is seen in more than half of all pregnant women In 32 per cent the condition was moderately severe and in 4 per cent severe [17] These figures were observed in Germany and may well differ from those of other countries



Fig. 218.—Xanthelasma, started in pregnancy

This gingivitis of pregnancy is primarily a connective tissue hypertrophy The inflammation seems to be secondary although it may dominate in the fully developed case It has been shown that similar hypertrophy of the gums can be produced in monkeys by injection of the concentrated urine of pregnant women. [749] Huber[1744] *found a high level (700 M U) of follicular hormone in one* liter of urine of a twelve-year-old boy who suffered from hypertrophy of the gums. Newborn children often show a comparable succulence of the oral mucosa which disappears within a few days leaving the empty suckling folds This may be one of the effects of the maternal or placental hormones. Vitamin C deficiency and hypocalcemia are accused by other mostly European dentists of being the main cause of gingivitis in pregnancy The proponents of this theory base their opinion on the low content of vitamin C in the serum of pregnant

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[1740] Portier J Gingivitis in Pregnancy Union méd. du Canada 65 645-646, 1936.

[1741] Monash, S Proliferative Gingivitis of Pregnancy *Cases, Arch. Dermat & Syph* 31 390-396, 1931

[1742] Schuch, J Schwangerschaftsgingivitis und ihre Behandlung mit Kalk und Vitamin C Arch f Gynäk 169 571-576 1939

[1743] Ziskin, D Blackberg S and Stout A P The Gingivae During Pregnancy Surg Gynec & Obst. 57 719-726, 1933

[1744] Huber H Zahnfleischerkrankungen in der Schwangerschaft Zbl f Gynäk 62: 1077 1091 1938

women suffering from gingivitis compared with normal controls, and on the therapeutic effect of vitamin C.

Many dentists advise treatment with Vitamin C and calcium. It is claimed to be helpful if the process is not too far advanced.[illegible] The teeth should be cleaned checked and treated at the beginning of pregnancy in order to minimize secondary infection. Only complications require local treatment.

The treatment of the dermatoses of pregnancy is both topic and systemic. The former is determined by the type and stage of the lesion. In the vast majority



Fig. 31. Severe acne eruption in pregnancy. There was almost no acne present before.

of the cases it is possible to keep the patient comfortable or to heal the eruption even during pregnancy. In the more severe and of course the dangerous cases the treatment should follow the methods described under herpes gestationis. Ringer's solution should always be tried first since it is not connected with any risk. Its antipruritic effect has been praised.[illegible] Injection of 1 to 5 c.c. of the

[illegible] Brauer, R.: Pregnancy Complications, Gingivitis, Med. Klin. [illegible], 19[illegible].

[illegible] Sala, S. L., and de Castellanos, S. P.: Treatment of Pruritus of Pregnancy With Ringer Solution, Semana méd. [illegible], 1937. [illegible], 1938.

patient's own blood has also been recommended.[1753] The serum of normal pregnant women should be given if Ringer's solution fails. In these cases the question of the artificial termination of the pregnancy will arise. In herpes gestationis the prognosis is favorable for the mother and less so for the child. These cases will rarely require the termination of the pregnancy. If the diagnosis of impetigo herpetiformis is made the pregnancy should be interrupted as soon as possible before large areas become involved and infected and make the operation dangerous. Even early abortion does not secure an absolutely favorable prognosis.[1754]

Influence of Pregnancy on Existing Dermatoses.—Pregnancy often influences the course of existing dermatoses. The observations regarding *psoriasis* are contradictory but improvement during pregnancy occurs quite often. The same is said of *acne* (Kaufmann in discussion to Seitz[1697]) but here too the observations are conflicting.[1696] The author has seen at least two cases of acne conglobata with severe exacerbations during pregnancy.

In several strikingly parallel instances patients with *alopecia* areata totalis regained their hair during pregnancy, only to lose it again a short time later. Seborrheic alopecia usually improves or is arrested.

Some contrasting observations on scleroderma and pregnancy have appeared (Jadassohn in Wiener[1697,1698,1699,1700]). (See scleroderma.)

Von Recklinghausen's disease often takes a turn for the worse in pregnant women.[1755]

[1753] Lysander, A.: Behandlung der Schwangerschafts-Dermatosen, Svenska läk.-tidning. 31: 33-39, 1934. Zbl. 49: 151.

[1754] Sharpe, J. G. and Young, R. H.: Neurofibromatosis. Effect of Pregnancy on the Skin Manifestations. J.A.M.A. 106: 683-683, 1936.

Chapter XXIV

CHILDBIRTH AND PUERPERIUM. THE SKIN IN THE NEWBORN

Childbirth and Puerperium

Emphysema.—In rare instances the intrathoracic pressure caused by the labor pains can puncture the lung tissue and press the air under the visceral pleura along the mediastinal spaces to the neck. Once such an air channel is formed more and more air is pumped into the loose connective tissue. Finally the subcutaneous tissue becomes inflated and painful and gives the palpating finger the crepitant sensation found in some chest injuries and in gas gangrene. The first symptoms of subcutaneous emphysema are most frequently found in the face, less often in the nape of the neck or above the sternum.[780] Some authors feel that the phenomenon is better explained by rupture of the tracheal wall due to the intense vibration caused by screaming. Pleural adhesions are also believed to play a part.[780,775] Only very rarely has an actual laceration of lung tissue been verified at autopsy (Depaul after Scheuer[1802]). Even laceration of the buccal mucosa with ensuing emphysema has been observed.[1786,1784] The clinical picture of the frog-like inflated neck, from where the emphysema may travel long distances under the skin, must be impressive, but even very experienced obstetricians have encountered it extremely seldom, about once in several thousand confinements. The patients were almost exclusively primiparae with pelvic contraction and very large babies. The prognosis of the emphysema per se is usually favorable.

Petechiae.—Since pregnancy creates a purpuric tendency, it is not surprising that under the strain of labor petechiae appear. They are most often seen in the conjunctivae and on the neck and shoulders, rarely over the entire body.[877,784]

Urticaria.—Urticaria beginning with labor and disappearing two days later has been seen.

Pruritus[786] and *Herpes* occur occasionally in the first day of the puerperium.

J. Jadassohn, personal communication, also author's cases.

[1784]Kosmak, G. W.: Cutaneous Emphysema During Labor. Bull. New York Lying-in Hospital 1907. Abstr. Zbl. f. Gynäk. 32: 1028, 1908.

[780]Briadetre, D.: Cervicothoracic Subcutaneous Emphysema. Case, Rev. de gynéc. et d'obst. 2: 183-185, 1912.

[775]Stoeckel, W.: Tratado de Obst., ed. 2, Vol. I, p. 207, 1932.

[1785]Stubbs, J. D. and Martin, H. E.: Traumatic Purpura Occurring During Labor. J. Obst. & Gynaec. Brit. Emp. 40: 303-304, 1933.

[786]Ruetsch, W. A.: Postnatal Complaints in 1000 Consecutive Cases. Illinois M. J. 74: 436-441, 1938.

Nail Hair —Not all the dermadromes of labor become immediately apparent. The great event leaves its mark on the growing tissues of the nails and hair but it is only considerably later that these sequelae become evident. From twenty-one to forty two days after the delivery transverse grooves or lines, very rarely only white stripes may appear on the proximal ends of all fingernails or on some symmetric nails. These lines which are known as *Beau s lines* are more pronounced on the nail of the thumbs and the first fingers than on the smaller



Fig 220



Fig. 221

Fig 220 —Hoof of an old cow showing periodical line formation (Courtesy University of Wisconsin, Department of Dairy Husbandry)

Fig. 221 — Horn of an old cow Physiological ring formation in regular intervals except on the free end which represents the oldest part of the horn formed during the first years of life The rings become less distinct the older they are (Courtesy University of Wisconsin, Department of Dairy Husbandry)

fingers. They are not always present but they are quite common They may occur after any acute disease and after gastrointestinal cardiac and other attacks. Therefore they alone cannot be regarded as a certain indication of preceding childbirth Since it takes about thirty days for the nail to appear under the edge of the cuticle and since the nail grows about 0 1 mm a day it seems easy to calculate retrospectively the day of delivery But individual differences in the rate of growth and other factors make a more accurate determination than the week of the event impossible [441]

Beau s lines also appear on the nails of the newborn (see newborn) Comparable to Beau s lines of the human nails ring formation on the horns of cows

after calving are commonly observed and used as an indication of age Similar marks are known to occur on the hooves of mares.

The growing *hair* is affected by the trauma of childbirth just as is the nail A considerable number of hairs are so weakened that they fall out after two to three months. Other hairs show only a thinned portion of varying length (Pohl-Pinkus mark) If the puerperium is complicated by fever and infection the mark may involve a longer stretch This mark is not only thinner but also lighter in color Considering the daily rate of the head hair growth as 0.3 — 0.5 millimeter or approximately 1 cm. per month[illegible] it is possible to determine the day of the delivery within certain limits. If several pregnancies follow each other closely the hair does not have enough time to recover and stays thin and short. Some veterinarians believe that animals who are prevented from eating the placenta lose much hair [illegible] even to the degree of complete epilation. Gross advises administration of 5 gm of placental extract three times daily for the treatment of post partum hair loss in women His series of 24 patients, afflicted with a condition which offers a good prognosis anyway needs confirmation on a larger scale

Skin irritations from the lochia and dermatitis around the nipples, shall be mentioned for the sake of completeness. Simunich noted in one thousand consecutive cases, the following postnatal complaints concerning the skin five cases complained of pruritus, four of which involved the extremities only one the vulva. There were four cases of excessive perspiration and four cases of herpes between the second and seventh days. In seven cases the axillary glands were swollen. Reports of infections of many kinds,[illegible] and onset of chronic diseases, are numerous, but no characteristic dermatoses seem to have been described in relation to this phase. Puerperal sepsis may exhibit itself in erythematous, morbilliform scarlatiniform and other rashes. Exfoliative dermatitis probably caused by Staphylococcus aureus hemolyticus has been seen [illegible] Purpura occurred also in the course of puerperal complications. Sensitization of a woman to her own milk, with allergic symptoms like urticaria and angioneurotic edema is considered possible though still lacking confirmation. [illegible]

The dermatoses of pregnancy usually subside in the postnatal period but *exacerbations in the early puerperium* are especially characteristic of herpes gestationis.

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*There are two types of ring formation on the horns of cattle. Normally rings appear at the base of the horn in both sexes every year after the third year It seems that they are caused by seasonal change of food. Besides this physiological ring formation, any event which depresses the metabolism of the animal deep enough may leave its mark on the growing horn. Such events may include disease, nutritional changes, and also pathological births. The normal births do not seem to cause rings. Analogous phenomena are important in the hair of sheep. Submaintenance nutrition causes thinning of the hair even to such an extent that the hair breaks off and the fleece may become lost. (Personal communication from Prof E Heizer Department of Dairy Husbandry University of Wisconsin.) (See also J Heller[illegible])

[illegible] Heller J Tierdermatosen, Handb d. H. u. Gk 14, 1 710-877 1930.

[illegible] Gross E. R. Dermatology in Relation to Endocrinology Clinics 3 812-832, 1944.

[illegible] De Lee J B The Principles and Practice of Obstetrics, ed. 7 Philadelphia and London 1938 W B Saunders Co.

[illegible] Binder A Exfoliative Dermatitis Due to Staphylococcus Aureus Hemolyticus During Puerperium. Zbl. f Gynäk 63 371-372, 1939

[illegible] Duke W W Allergy Asthma, Hay Fever Urticaria and Allied Manifestations of Reaction St Louis 1925, The C V Mosby Co

Psoriasis which quite often disappears in pregnancy commonly recurs during lactation

The Skin in the Newborn

The skin of the normal and fully developed newborn baby is red (erythema neonatorum physiologicum) and covered with vernix caseosa. The fetal lanugo hair has disappeared with the exception of some fuzz on the shoulders and on the back The head is usually covered with hair of up to one inch (2.5 cm) in length The eyebrows and eyelashes are developed. The nails have a palpable horny consistency and slightly exceed the fingertips in length The panniculus adiposus is well developed and causes characteristic bulges and folds especially on the buttocks and thighs.

Microscopically the horny layer of the epidermis is very thin [1766] and the nuclei stain well throughout the epidermis. [1766,1767] The papillae are flat but the papillary vessels are hyperemic. The tunica elastica of the blood vessels is well developed in contrast to the media and adventitia.[1767] The other elastic fibers are still but little differentiated [1768] It takes about three years until the elastic reticulum is developed approximately like that of the adult The corium is rich in cells. The fat cells have in contrast to the adult well-discernible nuclei The Pacinian corpuscles are completely differentiated In spite of the developed musculi arrectores pilorum goose flesh does not occur in the new born [1765] The hairs are devoid of a medulla

The sebaceous as well as the sweat glands assume their characteristic shape and full function after the fourth or fifth month [1765] of extrauterine life but secretion is present [1768] as early as the sixth month of embryonal life Milia neonatorum are either enlarged sebaceous glands or cysts filled with desquamated horn cells

The insensible perspiration is greater[1769] and the acidity of the newborn s skin is lower than in the adult The average pH of 6 7 is close to the neutral point [1770] Of course the transition from fetal to extra uterine life affects the whole system so profoundly that it is not surprising that it is recorded in the growing matrix of the nails. Schick[1771] determined the rate with which the physiological nail line of the newborn moves toward the free end of the nail. On the

30- 39th day the line has grown out 0.5 millimeter
40- 49th day the line has grown out 1 4 millimeter
50- 59th day the line has grown out 2.3 millimeter
60- 69th day the line has grown out 3.0 millimeter
70- 79th day the line has grown out 3.3 millimeter
80- 89th day the line has grown out 3 6 millimeter
90-100th day the line has grown out 4.2 millimeter

[1765] Gundobin, N P Die Besonderheiten des Kindesalters, Berlin, 1921 Allg Med. Verlagsanstalt

[1766] Tausch, M Die anatomischen Eigentümlichkeiten der Neugeborenenhaut und ihre damit verbundene Disposition zu Erkrankungen, Arch f Gynäk. 161 378-394, 1937

[1767] Chiale G Delle modificazioni dei vasi cutanei inerenti all'età Gior ital di dermat e sif 68 1635-1648, 1937

[1768] Meirer Kanai D Eigentümlichkeiten der Haut von Kindern, Orvosi Hetil 78 665-671, 1934; Zbl 49 495

[1769] Hecht, H Die Reaktionsfähigkeit der Haut beim Kinde Med Klin. 32: 769-700 1936

[1770] Taddei, A Ricerche mediante indicatori sulla reazione attuale della cute nel neonato Riv ital, Ginec 18 499-510 1935.

[1771] Schick, B Die physiologische Nagellinie des Säuglings, Jahrb. f Kinderh 67 146-160, 1908.

These figures were obtained from 250 measurements. Heller is skeptical about the practical value of these measurements since individual variations are common.

On the borderline of physiological and pathological peculiarities are the milia of the face, the symphysis praeputialis which disappears by desquamation the mongol spots and the superficial epithelial cysts in the midline of the hard palate.[1767] Several types of flat and faintly red telangiectases are known as nevi pallidi (stork bites) Unna s nevus is a relatively inconspicuous, macular purplish irregularly contoured telangiectasis of the nape of the neck. Other similar vascular maculae occur on the forehead [1768] on the eyelids and elsewhere. Most of these vascular nevi disappear spontaneously They should not be confused with true hemangiomas. Icterus neonatorum of varying degree occurs in about two out of three babies and clears up during the first week. A peculiarity of the infantile skin is its tendency to form blisters. Thus scabies in early childhood syphilis and even psoriasis may produce large blebs and the urticaria of this age often shows a central vesicle and a papular appearance giving it the characteristics of strophulus. The allergic skin reactions are likely to be vigorous or even violent so that a mild test reaction e. g a moderately positive Pirquet should be judged with great caution.[1769] Of great importance is the hemorrhagic tendency in the newborn In 66 per cent of the babies the endothelial permeability as measured by the number of petechiae elicited under controlled conditions by the application of a suction cup is increased above the adult level At the age of ten years this physiological hemorrhagic tendency has disappeared [1770]

The incidence of the more severe *hemorrhagic diathesis of the newborn* is about one in two hundred [1771] with a marked predisposition by asphyxia at birth The disease is not noticeable at birth On the third day symptoms of hemorrhagic disease such as the oozing of blood from the navel from circumcision and from other wounds or bruises may become manifest. There are often large purpuric spots but, according to Quick [999] petechiae are characteristically absent. Melena neonatorum is the most common type of the disease This trouble is due to hypoprothrombinemia. The prothrombin level at birth is near the adult level but it may fall during the first few days to as low as 10 per cent It returns to normal at the end of the first week.[999] The cause of this drop is a deficiency in vitamin K. The human body is unable to synthesize vitamin K which comes entirely from plants. The newborn is physiologically provided with enough vitamin K from the mother to tide him over the first week, until he can draw from the harvest of his intestinal flora which becomes established during this time. If the baby does not get enough maternal vitamin K or if his allotment is used up or destroyed before his own is ready for use the level falls below

[1767] Mayerhofer E Hauterscheinungen der Neugeborenen, Lijec'n. vjes 55 403-407 1933 Zbl 46 783

[1768] Hagenbach, M Ueber Teleangiektasien bei Neugeborenen, Ztschr f. Geburtsh u. Gynäk. 97 123, 1928

[1770] Bayer W Beitrag zu den hämorrhagischen Erkrankungen des Neugeborenen. Die Rolle der Endothelfunktion, Jahrb f Kinderh 133 223-235, 1931

[1771] Sanford L. Hemorrhagic Disease of the Newborn. 356 Cases, J Pediat 10 1 1941

the critical point and causes hypoprothrombinemia and hemorrhage Vitamin K restores the bleeding mechanism to normal. If 2 mg of vitamin K (menadione) are given to the mother within two days before delivery the baby s vitamin K ration is increased enough to prevent hemorrhagic disease.[1775] The modern treatment of hemorrhagic disease of the newborn has reduced the mortality from 57 per cent to 20 per cent.[1776]

A group of phenomena in the skin of the newborn is explained by the *effect of maternal or placental hormones* *The squamous epithelium of the vagina* of newborn girls develops a marked hyperplasia and becomes piled up to a thickness of 30-40 layers with the top layer constantly desquamating [1777 1778] The vaginal smear shows an abundance of naviculated squamous cells with pyknotic nuclei indistinguishable from the smear of pregnant women This phenomenon is clinically noticeable as a creamy white discharge rarely mixed with blood from the cervix A few days after birth regression of the hyperplastic epithelium sets in and the normal infantile vaginal mucosa develops. This phenomenon is so regularly found and so striking that it has been suggested to make use of it for the objective determination of the age of a newborn baby [1777]

Not as constant as the reaction of the vaginal epithelium but well known for ages is the swelling and secretion of the *mammary glands* in the newborn of both sexes (witch milk) The *linea alba* especially between the navel and mons veneris becomes pigmented in 8 per cent of the babies [1780] This pigmentation becomes visible at the age of three weeks and persists two to three months The succulence and sometimes even the swelling and fold formation of the *gums* in newborns (suckling folds) has been compared to the hypertrophic gingivitis of pregnant women[1778] (see pregnancy) The *labia majora* and also the *male genitals* of the newborn are often swollen and succulent This also may be due to hormonal influence Other influences of pregnancy have been observed in the internal genitals of male and female newborns [1779]

The comedones and the false milia i. e the enlarged sebaceous glands and the sometimes observed acne of the newborn (also his vigorous lanugo growth) have often been interpreted as hormonal pregnancy reaction One has even in view of the numerous gonadal stimulations spoken of a miniature puberty of the newborn The hypertrichosis of the newborn has also been called a parallel to the hypertrichosis of pregnancy [613,1780]

[1776] Dam H R The Fat Soluble Vitamins Handbook of Nutrition Chicago 1943, American Medical Association

[1777] Fraenkel L and Papanicolaou G N Growth, Desquamation and Involution of the Vaginal Epithelium of Fetuses and Children With Consideration of the Related Hormonal Factors, Am J Anat 62: 427 1938

[1780] Phillipp E Schwangerschaftsveränderungen beim Neugeborenen Klin Wchnschr 17 797 800, 1938

[1778] Neumann H Histologische und experimentelle Untersuchungen zur Frage der Schwangerschaftsreaktion der Neugeborenengonaden Arch f Geburtsh Gynäk 99 100-126 1930

[1779] Neumann H O Schwangerschaftsreaktionen im Neugeborenenorganismus Sitzungsb d Gesellsch Beford d ges Naturw zu Marburg 65 61 130 1931

[1780] Epstein, B Ueber ein neues Zeichen der fetalen Schwangerschaftsreaktion Acta paediat 11 100-106, 118-131 1930

[1781] Leiner C Hautkrankheiten im Säuglingsalter Handb d H Gk 11 1 490-537 1930

Chapter XXV

MENOPAUSE

The known physiological changes connected with the menopause are manifold The irregularity and the final ceasing of menstruation is due to ovarian changes which may precede the actual menopause for a considerable time. Failure of the formation of corpora lutea and simultaneous persistence of Graafian follicles is thought to be responsible for a temporary oversupply of estrin which may account for menopausal hemorrhage.[1783] The waning function of the ovaries is followed by excessive and persistent oversecretion and excretion of the luteinizing and follicle stimulating factors of the prepituitary [1784] This amount of anterior pituitary hormone which exceeds that in pregnancy by a wide margin disappears only slowly [1785] Injection of large doses of estrogen makes the gonadotropic factor temporarily disappear from blood and urine. In more than 50 per cent of the menopausal women as well as in castrates considerable quantities of the estrogenic factor circulate in the blood and are excreted in the urine.[1784] Along with the hormonal changes appear a great number of symptoms nervousness exhaustion headache insomnia depression arthralgia cardiac consciousness and obesity

Dermadromes.—Hot Flushes and Perspiration Formication.—In the skin hot flushes and excessive perspiration are the most common physiological phenomena of the change of life In evaluations of large series of the menopausal syndrome[1783, 1786, 1787] the incidence of hot flushes varies from 59 to 95 per cent This is understandable since the phenomenon is extremely variable in severity In the typical fully developed spell the patient, often after an abdominal aura suddenly suffers from a sensation of heat which is described as creeping from the lower parts of the body to the head The face is usually flushed In severe attacks the patient has the urge to open her dress and seek an open window in order to satisfy the sensation of air hunger After a short period of about twenty seconds to three minutes the attack ends with a profuse perspiration which often causes chills. Fortunately such severe seizures are relatively infrequent and the vast majority of women experience only milder flushes. The number of attacks varies from a dozen times a day for several years to a few attacks which almost pass unobserved. The flushes (also called flashes) seem to be a most dependable indication of the cessation of normal ovarian function In many

[1783] Lewis T F Symposium Menopause-Disorders, Rev M Progr pp 86-87 1940

[1784] Frank R T Goldberger M A and Salmon, U J The Menopause Symptoms, Hormonal Status and Treatment New York State J Med 36: 1-9 1936

[1785] Von Haam E Laboratory Diagnosis of Menopausal and Climacteric States, Rev M Progr pp 90-92, 1940

[1786] Hawkinson, L F Menopausal Syndrome 1,000 Consecutive Patients Treated With Estrogen, J A M A 111 390-393, 1938

[1787] McDowell, J G and Paterson, A S Physical and Psychologic Symptoms of the Menopause, J Obst & Gynaec Brit Emp 47 319-334, 1940

cases in which deep X ray therapy was directed to still functioning ovaries mostly because of pelvic malignancy the author hardly ever observed the onset of the induced menopause without flushes. On the other hand if flushes failed to be noticed the sterilization was usually not accomplished Reynolds showed that the menopausal flush is caused by arteriolar dilatation He demonstrated in plethysmographic tests that the injection of estrogen in menopausal women is followed by a plateau type of vasodilatation This reaction does not cause any sensation While the plateau type response is developing a sharp increase in the tested finger volume may occur and last from three to fifteen minutes. During this flush type reaction the skin temperature is elevated and the patient has a sensation of heat. Excessive perspiration and formication is a complaint in about one third of the cases. [784]

Hypertrichosis.—While flushes and perspiration have a physiological character a great number of dermatoses have been related to the menopause On the borderline between physiological and pathological dermadromes is



Fig 222 Climacteric hypertrichosis

the hair growth which sometimes appears as a more marked lanugo on the upper lip and sometimes as more or less numerous thick dark bristles on the chin and in the ears. At the same time the hair on the scalp as well as the axillary and pubic hair loses much of it vigor and becomes scanty and thin In rare cases the menopausal hair growth may assume the character of a true beard which embarrasses the unfortunate woman to an extreme degree The menopausal

facial hair growth shows a remarkable similarity to the scattered "beard" of the male castrates. It seems that the functioning ovary affords a certain protection against the hair growth stimulating effect of the adrenals. In two cases of the literature menopausal facial hair growth was strongly stimulated by ovariectomy In one of these remarkable cases the patient had to shave twice daily and in the other the woman made the best of her condition by exhibiting herself as a bearded woman in the side show of a circus [1775] Rosenhagen tried to solve the pathogenesis of the menopausal beard by paying special attention to this question during autopsies on women above the age of thirty In thirty cases with marked beard growth the ovaries and adrenals were separated from fat weighed and histologically examined In five cases adenomas of the adrenal cortex were found but the remaining twenty five did not yield any tangible findings. Perhaps the shift in the relation between the still vigorous adrenals and the atrophying ovaries suggests an explanation [1776,1777] But if so why does not the menopausal hypertrichosis appear more frequently? Another suggested cause is the elevated prolan level in the blood and urine, which together with hypertrichosis, is also found in the basophile adenoma of the anterior pituitary

Pigmentation Benign Cutaneous Neoplasms.—Changes in the pigmentation and chloasma resembling spots, as well as depigmentations occur quite frequently [1778]

Stimulation of the growth of small soft cutaneous fibromas and moles is common It may be explained by the oversupply of prolan Similar phenomena can be observed in pregnant women The so-called cutaneous tags or small fibromata pendula around the neck are very common in menopausal and especially obese women.

Obesity—The panniculus adiposus is very often increased Careful study of the blood chemistry basal metabolism etc. has so far failed to find the cause [illegible] Some women become thinner with the change of life

Pruritus Vulvae Leukoplakia. Kraurosis—Pruritus vulvae is common in the menopause. There are many causes or combinations of causes which may lead to pruritus and its related conditions. The most common irritations those caused by discharge and infected urine[1779] do not strictly fall into the scope of this book. Oxyuriasis does not seem to play a major role in vulvar pruritus of the menopause, but *mycotic infection is very common in* America in contrast to Europe

Latent diabetes with or without sugar in the urine often causes pruritus vulvae [1780] Coincidence with the menopausal age may often cause the physician

[1775] Kovacs, F Beitrag zur Pathologie des Hirsutismus und Virilismus, Monatschr f Geburtsh. Gynäk 91 65-78, 1932.
[1776] Berblinger W Klimakterische Gesichtsbehaarung und endokrine Drüsen, Ztschr f. d. ges. Anat Abt 2 Ztschr f Konstitutionsl 10: 413-423, 1924
[1777] Berblinger W B Zur Frage der Gesichtsbehaarung bei Frauen Ztschr f d ges Anat., Abt. 2 Ztschr f Konstitutionsl 13: 193-214, 1928
[1778] Marzetti and Fellner M Haut und Klimakterium, Endokrinologie 8 8 121 1931
[1779] Savill A Treatment Pruritus Vulvae Brit J Derma 52: 32 -233 1 40
[1780] Wisser L H and Strahauch, E. A. Vulvar Pruritus as Possible Early Symptom of Unrecognized Diabetes, Journal-Lancet 60: 433-434 1940.

to treat such patients with hormones instead of applying more sensitive tests for detecting diabetes. It seems as though the part which the various etiologic factors have been accused of playing depends on the various authors. Still after the deduction of all the readily explainable cases of pruritus vulvae there remains a group which can be linked to hormonal disorders as was suggested a long time ago [illegible] mainly because of coincidence with menstruation hypomenorrhea[illegible] and particularly the menopause and castration [illegible]



Fig 223 Kraurosis vulvae

Lately based on blood assays unexpectedly high estrogen values in the menopause have been found together with pruritic conditions of the vulva [illegible] The frequent reports of successful treatment with estrogens have done much to establish the general opinion of a hormonal etiology

It has been attempted to separate chronic pruritus vulvae leukoplakia and kraurosis. Since transitional pictures are common and the same case may in its course pass through all the varieties it is justifiable to deal with them

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[illegible] Brocq L Kraurosis, Bull. Soc. franç d dermat. et syph 1912 also Ann de dermat. et syph Abstr Dermat Wchnschr 62 305, 1916

[illegible] Taussig Precancerous Lesions of the Skin of the Vulva Leucoplakic Vulvitis Kraurosis Pruritus, Arch Dermat & Syph 1 621-635, 1920

[illegible] Ferrari, A B Presentazione di case clinico, Gior ital. di dermat. 68 1466-1467 1927

[illegible] Labhardt A Pruritus Vulvae Etiology and Therapy Sch el med W hnschr 70 1212 1214, 1940.

[illegible] Terruhn, E Kraurosis Vulvae Arch f Gynäk. 151 578, 1932

[illegible] Shute, E Degenerative Vulvar [illegible] Associated With Estrogen Imbalance J Obst & Gynaec. Brit. Emp 49 482-495, 1942

together The disease starts with a subacute dermatitis of the vulva and often of the perianal area. There are exacerbations with oozing and widening of the involved area, followed by regressions. Secondary infection especially folliculitis and irritation from scratching is common A certain percentage of the cases may heal in this stage while others may develop a condition which is quite different from chronic eczema. The skin which was red and succulent before gradually acquires a leathery rigid character and cracks easily It becomes more and more depigmented pearly or bluish white and dry The hair the labia minora and the clitoris disappear Finally atrophy of the vulva with white thin skin develops. The introitus vaginae may become contracted. Pruritus is present in all stages, and on close inspection leukoplakia can be found in almost every instance.[1799] It is from these leukoplakic patches that cancer develops in more than fifty per cent of the cases. The histologic picture corresponds to the described clinical sequence. Hyperkeratosis acanthosis, and inflammatory infiltration of the upper derma is followed by thinning of the epidermis, and loss of pigment and elastic fibers. The papillae disappear completely Many patients with chronic vulvar eczema never develop leukoplakia and kraurosis and cancer is rare in these nonleukoplakic cases.

Treatment of the pruritus vulvae, based on the elimination of the mentioned etiologic factors, is not often possible. Besides various local procedures, estrogen therapy should be tried. The dosage advised has become higher and higher Foss[1800] starts the treatment with injections of from 10 to 25 mg of estradiol benzoate twice weekly As improvement occurs the injections are reduced to one a week. Smaller doses are necessary if local treatment in the form of ointment containing estrone, estradiol or estradiol benzoate is used Foss gives the following formula for the ointment

Estradiol benzoate consisting of	10 milligrams in sesame oil mixed with 100 grams of base	
	Halibut liver oil	20 parts
	Cerae albae	16 parts
	Adipis lanae	2 parts
	Sodium biborate	1 part
	Ol. amygdalae	41 parts
	Aquae	20 parts

A great number of similar creams have been advised [1801-1804] The massaging into the thoroughly cleansed skin of 0 5 mg of estradiol in sesame oil seems a practical method [1804] This should be done once daily by the physician Later the patient may follow it up with an estrogen cream.

[1800] Foss, G. L. Further Developments in Treatment (Pruritus Vulvae) J. Obst. & Gynaec. Brit. Emp. 46 371 395 1939

[1801] Klaften, E. Treatment of Essential Pruritus and Kraurosis Vulvae by Simultaneous Local and Parenteral Administration of Estrogen. J. Clin. Endocrinol. 3 318-322, 1943.

[1802] Loboeve I. I. Stilbestrol (Estrogen) Cream in Pruritus, Urol. & Cutan. Rev 45 314-315 1941

[1803] Schrattenbach T. Oestroglandol (Estrogenic Preparation) in Therapy of Pruritus Vulvae, Wien. med. Wchnschr 86 905-906 1936.

[1804] Kervorkian A. Y. Treatment of Chronic Pruritus With Local Applications of Estrogen, New England J. Med. 220 641-642, 1939.

Suppositories containing 0.36 mg. of di-hydro-oxygestrin in 2 grams of cocoa butter have been found effective when inserted into the vagina once or twice daily.

It seems as if the initial enthusiasm about the hormone therapy of vulvar pruritus is subsiding.[illegible] It is certain that estrogen therapy not infrequently fails. The difficulty of finding out the suitable cases has led to the unsuccessful treatment of many cases. It is furthermore agreed that only few patients achieve complete and lasting comfort. Relapses, which require further local therapy or a few injections, are common. The more severe cases need almost continuous substitution therapy in one form or another.[illegible] Some authors are reluctant to administer the estrogen locally over a long time because of the danger of producing cancer in a condition which is precancerous in itself. Finally, adverse effects like uterine bleeding in menopausal women and local exacerbations are known to occur. However, the fact remains that estrogenic therapy in many cases is one of the best methods we have for giving relief in a very annoying condition.

Similarly as in neurodermitis, to which pruritus vulvae has other parallels, the gastric hydrochloric acid has been found low or completely lacking in about one out of three cases. The more severe cases of kraurosis and leukoplakia are associated with achlorhydria.[illegible] These cases seem to be benefited by regular HCl medication. Vitamin A in any convenient form[illegible] and vitamin E or wheat germ oil in very high doses[illegible] as well as vitamin B_1[illegible] and uncooked diet have been recommended, but not enough convincing experience has been forthcoming.

In discussing the internal therapy of the pruritic conditions of the vulva, the importance of the various local methods such as antipruritic salves and lotions, surgical procedures, and radiation therapy should not be forgotten.

Miscellaneous.—The great number of cases of eczema, herpetiform eruptions, pruritic attacks, and other dermatoses which have been labeled as menopausal because they appeared in women at the age of forty to fifty-five have rarely been investigated closely enough to corroborate this claim. Naegeli and Fellner[87] believe in a higher cutaneous sensitivity in the menopause just as is present during menstruation. This is supposed to account for many of the eczemas in middle aged women. High urinary prolan does not prove more than the onset of the menopause and therefore does not confirm gonadal origin of the dermatosis in question. The best though still not a perfect proof is prompt cure after treatment with estrogen.[87]

[illegible] Hu, III A. Pruritus Vulvae, Leukoplakia and Kraurosis, J. Obst. & Gynaec. Brit. Emp. 49: 310-327, 1942.

[illegible] Reis, R. Pruritus, Leukoplakia and Kraurosis in Patient Aged 65, S. Clin. North America 20: 107-116, 1940.

[illegible] Swift, B. H. Achlorhydria and Pruritus Vulvae, J. Obst. & Gynaec. Brit. Emp. 43: 1053, 1936.

[illegible] Kusera, D. Pruritus Vulvae, Vitamin A and Vitamin B_1—Complex in Therapy, Zbl. f. Gynäk. 66: 922-927, 1942.

[illegible] Fymer, H. Pruritus vulvae, Deutsche med. Wchnschr. 68: 941-942, 1942.

[illegible] Leszczynski, R. and Liebhart, S. Dermatosen bei Frauen auf hormonaler Grundlage, Przegl. dermat. 26: 213-259, 1931; Zbl. 41: 79, 1932.

A tendency to *edema* in various forms is an often mentioned climacteric *manifestation*. There are *slight fugitive edemas* of the extremities and also of the face which develop over night and disappear during day time.[illegible] Angioneurotic edema (Quincke's edema) is undoubtedly more common in the menopause and may then respond to hormonal therapy.

Urticaria factitia and an urticarial character of various types of dermatitis is often mentioned in connection with the menopause.



Fig. 224



Fig. 225

Figs. 224, 225. Keratoderma climactericum (Haxthausen): discrete palmar hyperkeratoses showing absence of [illegible] frequently with obesity and hypertension following menopause. (Courtesy Dr. H. Haxthausen, Copenhagen, Denmark.)

Haxthausen[illegible] described a *keratoderma climactericum*: ten cases of a dermatosis which he observed in women who besides the symptoms of menopause showed some degree of obesity, a normal basal metabolism, arterial hypertension and occasionally arthritis.

In the early stages the skin changes consist of lentil size, discrete, scaly keratoses apparently without inflammation. They are seen on symmetric spots of the palms and soles. Later they can hardly be differentiated from eczema.

[illegible] [illegible], H.: Ueber klimakterisches Oedem. Med. Klin. [illegible]: 1370-1371, [illegible].
[illegible] Haxthausen, H.: Keratoderma Climactericum. Brit. J. Derm. 46: 161, 1934.

The relative frequency of *pemphigus* in the menopause has been emphasized.[1833] The author is inclined to confirm this impression.

Rosacea and telangiectases are often mentioned in connection with the menopause. The same applies to Fox Fordyce disease, to Poikiloderma atrophicans vasculare, calcifications of the skin, acrodermatitis atrophicans, Raynaud's syndrome, scleroderma, erythema perstans, trophedema,[1834-1836] xanthelasma and other dermatoses.

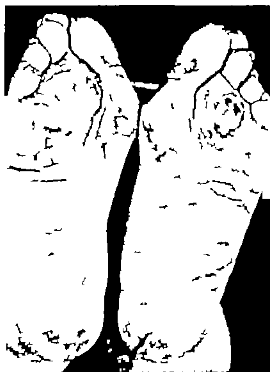


Fig. 226. Keratoderma climactericum (Haxthausen). (From Lynch, F. W.: Arch. Dermat. & Syph., 1943.)

[1833] Werther, J.: Pemphigus, Arch. f. Dermat. u. Syph. 151: 179, 1926.

[1834] Milroy, F. W.: An Undescribed Variety of Hereditary Edema, New York M. J. 56: 505, 1892.

[1835] Milroy, F. W.: Chronic Hereditary Edema, J. A. M. A. 91: 1172, 1928.

[1836] Chvostek, F.: Xanthelasma und Ikterus, Ztschr. f. klin. Med. 73: 479, 1911; Wien. klin. Wchnschr. 23: 1630-1635, 1910.

[1837] Adlersberg, D.: Befund bei einer ... Xanthoma ..., Arch. f. Dermat. u. Syph. 149: 400, 192[illegible]

Chapter XXVI

MISCELLANEOUS DERMATOSES WITH ENDOCRINE BACKGROUND

Dermatitis Dysmenorrheica Symmetrica.—In 1912 Matzenauer and Polland[illegible] published six cases of an unusual dermatitis in dysmenorrheic, mostly young girls. The attacks or crops were not in connection with the menses. The lesions appeared in patches which were mostly round on the trunk and more oblong on the extremities. They were approximately symmetrical except in or close to the midline. The individual lesion started with a burning sensation followed by a pale red urticarial erythema, the tinge of which was different from the early stage of ordinary dermatitis. Within half an hour the urticarial infiltration made the follicles stand out. Serum exuded into the follicles and formed a thin yellowish crust on the follicular orifice. These follicular lesions often coalesced within a few hours to form large weeping or crusty patches which were still slightly elevated because of their urticarial component, and surrounded by a narrow inflammatory margin. Follicular extravasations often gave the patch a characteristic dotted appearance. The varying intensity of the changes could produce all degrees of inflammation running the gamut of exudative and hemorrhagic stages to the severe destruction of connective tissue with scar formation. The lesions healed quickly within a few days unless deeper destruction occurred which was rare. In these cases the picture and course was that of a dry necrosis and slow demarkation caused by an anemic infarct. The patches appeared most often on the face and less often on the hands, arms, legs and upper trunk. In one case the oral and laryngeal mucosa was involved.

Looking at the pictures of the original article one cannot help thinking of artifacts produced by striking or rubbing the skin with the fingers. The authors were fully aware of this impression and did everything imaginable to rule out self inflicted lesions.[illegible] They observed some patches developing while the patient was asleep or under impervious dressings of zinc-gelatin. The buccal and laryngeal lesions certainly could not be self-inflicted. When a lesion was observed to appear on one leg the corresponding spot of the other leg was immediately covered by a zinc-gelatine dressing. When this dressing was removed after two hours of constant medical watching a typical patch was found. It was impossible to produce typical lesions by mechanical and electrical irritation by spraying with ethyl chloride or by other methods.

All patients were suffering from *dysmenorrhea*. The menses were irregular connected with many complaints and the flow scanty. Puberty and the onset

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[illegible] Matzenauer, R. and Polland, R. Dermatitis Symmetrica Dysmenorrhoica, Arch. f. Dermat. u. Syph. 111: 385, 1912.

[illegible] Polland, R. Neue Beiträge zur Klinik der Dermatosis dysmenorrhoica, Arch. f. Dermat. u. Syph. 131: 453-460, 1921.

small patch hidden under the hair to the size of a whole leg. The spots are often found on the nape of the neck, on the lower back, and on the buttocks. They resemble the milk coffee spots seen in von Recklinghausen's neurofibromatosis. These areas of pigmentation indicate some relationship to the skeletal involvement. Unilateral bone disease is usually accompanied by ipsilateral pigmentations; widespread bone lesions by numerous and large pigmentations.

Fig. 223.—Albright syndrome. Note areas of pigmentation. (Courtesy Wisconsin General Hospital.)

The blood calcu ... od ... e normal; this is important in the differentiation of hy ... of at least twenty five recorded exp ... never been found. The differ ential ... is ... osis. H ... Christian's xanthe ... omas ... and some other ... disease pig-

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All patients were suffering from *dysmenorrhea* The menses were irregular connected with many complaints and the flow scanty Puberty and the onset

[817] Matzenauer R., and Polland, R Dermatitis Symmetrica Dysmenorrhoica. Arch f. Dermat. u. Syph. 111: 385 1912.

[818] Polland, R Neue Beiträge zur Klinik der Dermatosis dysmenorrhoica. Arch. f. Dermat. u. Syph. 131: 452-460, 1921

of menstruation had often been late in one case precocious Psychopathic stigmata and functional circulatory disorders were noted

There is no doubt that the syndrome described by Matzenauer and Polland is an unusual one It must be very rare and the geographic distribution very uneven While the six original and two of the later cases of the conspicuous dermatosis were seen in the clinic in Graz Austria almost all the other cases so far about forty were seen in European and American centers which handle great numbers of patients. Only part of the forty cases published so far closely resemble the original description [1879-1884] The classical clinical picture of round oblong or fingershaped symmetrical patches does not seem to be a requirement anymore since cases of various types of dermatitis associated with ovarian disorders have been published as dermatitis dysmenorrheica This has apparently been done with the consent of Polland who in 1935 in an abstract written by him did not object to Urbach's [1879-1884] including some cases of erythroderma and neurodermatitis into the syndrome called Dermatitis dysmenorrheica

This depreciation of the morphology has come about by the progress achieved in determining the etiology of the menstrual dermatoses Urbach believes that the reactivity of the individual determines the morphology of menstrual dermatoses of a given dyshormonal causation Thus today the term dermatitis dysmenorrheica includes various dermatoses associated with menstrual disorders

Urbach and Kitamura [1884] in their case of menstrual neurodermatitis labeled as dermatitis dysmenorrheica found the urinary excretion of gonadotropic substances increased while the estrogen content of the urine appeared to be lower than normal The patient was improved by estrogens and progesterone also by bleeding and laxatives. The effect of the latter kind of treatment suggests a toxic factor According to Urbach it is occasionally possible to demonstrate that in dermatitis dysmenorrheica the premenstrual blood contains a substance which when injected into the skin of the patient during the intermenstruum will evoke an immediate urticarial reaction and a delayed response in the form of pinpoint-sized papules clinically resembling the menstrual dermatosis. Such a reaction could not be elicited in the patient with her own intermenstrual serum or with premenstrual serum from normal women Normal control persons did not respond to the premenstrual serum of the patient Probably as in the other menstrual dermatoses allergic as well as toxic, and possibly neuro-psychogenic factors may be of importance Pregnancy and cessation of the menses

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[1879] Friedeberg J Dermatitis symmetrica dysmenorrhoica Arch f Dermat u Syph 111 173-184 1912

[1880] Wise F and Parkhurst So-Called Dermatitis Dysmenorrheica, Arch Dermat & Syph 2 723 1920

[1881] Wirz F Gibt es eine spezifisch dysmenorrhoische Hautkrankheit? Arch f Dermat u. Syph 136 36-47 1921

[1882] Hauck L Beitrag zur Dermatitis symmetrica dysmenorrhoica (Matzenauer-Polland) Wien. med Wchnschr 75 3 6-3 79-453 1925

[1883] Lindner L Ueber die sog Dermatitis symmetrica dysmenorrhoica, Diss Erlangen 1922 Zbl 16 906

[1884] Urbach, E and Kitamura, Ueber pathologische Ausscheidung von Sexualhormonen bei einem Falle von Dermatitis dysmenorrhoica Polland Matzenauer) Klin Wchnschr 11 271 274 1935

prevents the attacks. This has been demonstrated in several instances when after failure of other measures X ray castration was resorted to [illegible]

In several cases monthly attacks preceded the unusually late menarche and failed to appear later [illegible] In two cases of symmetric dermatitis dysmenorrheica marked prolanuria could be demonstrated. [illegible]

The treatment should tend to correct any endocrine disorder If this fails the desensitization with premenstrual blood after the methods of Geber and Lehner and Rajka should be tried (see menstruation) Estrogen salve (5000 units per gram of Aquaphor) has been claimed to be successful locally [illegible] Castration must be reserved for severe and intractable cases

Fox Fordyce Disease.—The dermatosis in question is a chronic, symmetrical papular itching eruption involving the armpits and the pubic area. The axillary lesions form a diamond-shaped palm-sized group of closely set yet discrete, firm, shotty perioral papules of pinhead to pea size. The papules are of normal or pink color only little excoriated and mostly arranged in beaded rows which cross the axilla. These grater like rows can be well demonstrated by stretching the skin This dermatosis is, with rare exceptions, extremely itchy so that the axillary hair is usually rubbed off Similar lesions occur though much less often in the pubic area and in the skin of the external genitalia and the navel.[illegible]

The pathologic changes consist of acanthosis parakeratosis keratosis and inflammation mainly surrounding the openings and lining the ducts of the apocrine sweat glands and of the hair follicles. The orifices of the involved glands are usually blocked by a keratotic plug

The disease is quite rare and seems to affect pigmented races more often e.g the Negroes and Jews (Jadassohn in discussion [illegible]) Only in a few (4) instances has it been observed in the male. [illegible] The eruption is almost exclusively a disease of the menarche It has never been seen before puberty at which period it sometimes starts [illegible] The menopause may bring the trouble to an end [illegible] but the disease may also be provoked at this time.[illegible] The dis-

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[illegible] Berde K. Fall von Toxicoderma menstruale mit erysipeloidartigen Erscheinungen, Orvosi hetil. 69 201-203 1925 Zbl. 18 435.

[illegible] Tragan J Die dysmenorrhoische symmetrische Dermatitis (Pellizzarische Krankheit), Rev méd. de Barcelona 4 424, 1925 Zbl. 20 60 1926

[illegible] Tramant, J., jr Die symmetrische dysmenorrhoische Nekrose Crón. méd. mexicana 28: 10-14, 1926 Zbl. 21 204 1927

[illegible] Artom, M. Considerazioni cliniche ed endo-pa ...che intorno alle dermatiti dismenorroiche Arch ital di derma ... 6 413-460 1931

[illegible] Reifferscheid W Zur Behandlung ovariell bedingter Dermatosen mit Follikelhormon ... München med Wchnschr 84 1700 1937

[illegible] Alexander A Fox Fordyce sche Krankheit Handb d. H. Gk. 8 1 423-441 1927

[illegible] Pick, W Zur Pathogenese der Fox Fordyce schen Krankheit, Arch. f. Dermat u Syph. 164, 168, 1930

[illegible] Kaufman, S M Fox-Fordyce's Disease in Male New York State J Med. 31: ... 1931

[illegible] Steiger Kazal, D Fox-Fordyce-Erkrank ... Zbl 35 484 1930.

[illegible] Sperber S Fox Fordyce Disease Arch. f Dermat u Syph. 178: ... 1938.

[illegible] Oeri München med Wchnschr 79: 533 1932.

[illegible] Dowling, O B and Forman, L Fox Fordyce Disease Proc. Roy Soc. Med. 25: ...-1072, 1932.



Fig. 227



Fig. 228

Figs. 227, 228. Fox-Fordyce disease. (Courtesy Dr. Frank Vero, Vanderbilt Clinic, New York.)

order seems to improve in pregnancy.[illegible] Ovarian deficiency with amenorrhea, dysmenorrhea, infantilism, cystic ovary and other sexual dysfunctions have been described in the great majority of cases.[illegible] Premenstrual and menstrual exacerbations which may climax in violent pruritic spells is often mentioned. Hyperthyroidism[illegible] and hypothyroidism[illegible] have been found much less often than ovarian deficiency.



Fig. [illegible] —Fox-Fordyce disease. Extremely itchy [illegible] order [illegible] -ray treatment.

Considering the well known sexual relationship of the apocrine glands (see Puberty) and the evidence of accompanying ovarian disorders, an ovarian etiology seems very probable. This is further supported by the response to estrogen therapy and in some cases proluton therapy.[illegible] Some authors believe that the condition is not curable and others think that roentgen therapy is the most effective treatment.

[illegible] Gougerot and Blum, P.: Maladie de Fox-Fordyce non prurigineuse, Bull. Soc. franç. de dermat. et syph. [illegible] 700-701, 1932.

[illegible] Lortat-Jacob and [illegible], U.: [illegible] de maladie de Fox Fordyce, Bull. Soc. franç. de dermat. et syph. [illegible] 12, [illegible]

[illegible] [illegible], D.: Fox-Fordycesche Krankheit, Zbl. [illegible] 124, 1931.

[illegible] [illegible]: Fox-Fordyce Disease, Arch. Dermat. & Syph. [illegible] 872, 1935.

[illegible] Goodman, M. H. and Solomon, M.: Fox-Fordyce Disease (Estrogenic Studies), Arch. Dermat. & Syph. [illegible] 907, 1939.

[illegible] [illegible], J.: Hormonal Dysfunction in Fox-Fordyce Disease, [illegible] 300-[illegible] 1936. Abstr. Dermat. Woche. [illegible]

[illegible] [illegible]: La maladie de Fox-Fordyce, Ann. de dermat. et syph. [illegible] 1931.

[illegible] [illegible], F.: Corpus Luteum Hormone Therapy [illegible] München. med. Wchnschr. [illegible]: 42-43, 1940.

[illegible] Roxburgh, A. C.: A Case of Fox-Fordyce Disease, Brit. J. Derm. [illegible] 121, 1943.

[illegible] [illegible], O.: Sex Hormones in Therapy of Fox-Fordyce Disease, Dermat. Wchnschr. [illegible] 723-726, 1941.

Albright's Syndrome.—This typical combination was first recognized by Fuller Albright[1847] who described a triad of disseminated osteitis fibrosa, areas of cutaneous pigmentation which have a distribution suggesting some connec-



Fig. 230.—Albright's syndrome. Areas of pigmentation and precocious puberty. (From Albright, F., Butler, A. M., Hampton, A. O., and Smith, P.: New England J. Med.)

tion between them and the bone lesions, and sexual and somatic precocity when the disease occurs in the female sex." Pathological fractures are common.

[1847] Albright, F., Butler, A. M., Hampton, A. O., and Smith, P.: Osteitis Fibrosa Disseminata, Areas of Pigmentation and Endocrine Dysfunction With Precocious Puberty in Females, New England J. Med. 216: 727-746, 1937.

According to Lichtenstein and Jaffe [149] who reviewed ninety cases among them fifteen of their own the syndrome is not extremely rare if one includes the in complete cases. The disease affects girls more often than boys the ratio being about 3:2. The first symptom is often a pathological fracture which leads to x-ray examination of the bones. Scattered but often unilateral patchy cystlike lesions of osteitis fibrosa are found. There are always parts of the skeleton show ing normal bones.[149, 150]

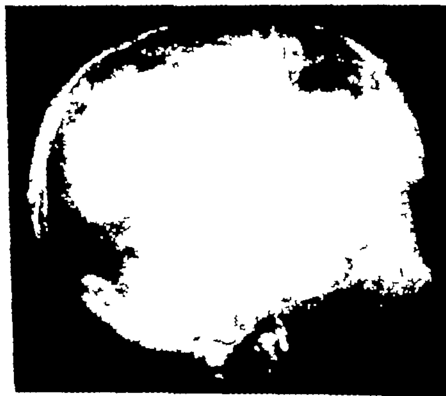


Fig. 13. [illegible] syndrome [illegible] fibrosa disseminata. From Albright, F.: New England J. [illegible]

In the female sexual precocity with early onset of menstruation and development of secondary sex characteristics and early bone age occurs in about one third of the cases.[150] The sexual development in the male patients is normal. In the [illegible] smooth brown nevus like patches of oblong round or [illegible] shape. The [illegible] from a group of freckle like spots or a single

[149] Lichtenstein, L., and Jaffe, H. L.: Fibrous Dysplasia of Bone. Condition Affecting One, Several or [illegible] Bones, [illegible] Abnormal Pigmentation of Skin, Premature Sexual Development [illegible] Hyperthyroidism [illegible] 33: 777 [illegible] 942.

[150] [illegible] Differential Diagnosis of Hyperparathyroidism With Especial Reference to [illegible] Syndrome. New York [illegible] J. Med. 43: [illegible] 944.

[illegible] Dashaber[illegible] L. and East, N. R.: Albright Syndrome [illegible]

small patch hidden under the hair to the size of a whole leg The spots are often found on the nape of the neck on the lower back, and on the buttocks. They resemble the milk coffee spots seen in von Recklinghausen s neurofibromatosis. These areas of pigmentation indicate some relationship to the skeletal involvement. Unilateral bone disease is usually accompanied by ipsilateral pigmentations widespread bone lesions by numerous and large pigmentations.

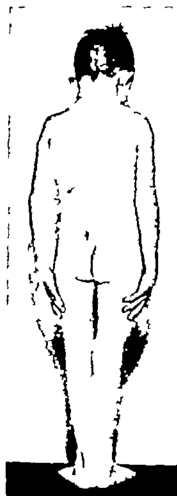


Fig 232 Albright syndrome Note area of pigment in leg. (Courtesy Wiesmal General Hospital)

The blood calcium and blood phosphorus are normal this is important in the differentiation of hyperparathyroidism In spite of at least twenty-five recorded explorative operations a parathyroid tumor has never been found The differential diagnosis has to rule out neurofibromatosis *Hand Schüller Christian s* xanthomatosis Paget s disease multiple hemangiomas of the bones and some other rare condition The diagnosi i ea y if the classic triad of bone disease pig

mentation and precocity in the female is present. Several patients started life with icterus gravis neonatorum which persisted for months.[illegible, illegible]

The etiology is unknown. An embryonic defect (Albright) seems likely. The twin brother of one patient was normal. In some cases a positive Babinski suggests a participation of the nervous system.[illegible]

The prognosis of the disease should be guarded but not too pessimistic. In one case precocious puberty was followed by normal adult sex life with the consequent production of a healthy child. The bone disease may become arrested. The individual bone lesion is amenable to surgical treatment.

It is of interest that Lena Medina of Peru, who gave birth to a child at the age of five, probably represented such a case of Albright's syndrome. Her attending physician, Dr Gerardo Lozada of Pisco, Peru, informed Dr Albright that she had both the brown spots and bone changes together with the precocity.

Geroderma Genito-Dystrophicum. Progeria.—In this rare syndrome, which has been seen starting early in life in both sexes, the most striking feature is the senile appearance of the skin and particularly of the face. There are many fine wrinkles; the skin is flaccid, yellowish, and the subcutaneous fat and the muscles on the distal parts of the extremities are usually extremely reduced. The hair is either completely lacking or restricted to the scalp. The skin gives a senile atrophic impression which make children or relatively young persons look old. Diffuse and early arteriosclerosis is a characteristic feature. Generalized pigmentation has been seen. The nails are thin and brittle. The skeleton is either eunuchoid or dwarfed. The intelligence is intact. Many endocrine symptoms like diabetes insipidus, exophthalmos, polyphagia and amenorrhea have been described. The testicles are atrophic. Aplasia or atrophy of the thyroid and tumor or sclerosis of the pituitary have been found at autopsy. The disorder is probably related to *Simmond's disease in which precocious senility* is also a feature.[illegible] In spite of the severe changes, the mentality remains alert and the patients may live for many years.[illegible, illegible] A syndrome of infantilism with web formation of the skin along the neck is known as *Turner's[illegible] syndrome*. In one autopsy case[illegible] no functioning ovarian tissue could be found. There was no axillary hair present and the pubic hair was scanty.

Scleroderma, Poikiloderma, Acrodermatitis Atrophicans.—The voluminous literature on these rare dermatoses is replete of reports on accompany-

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[illegible] Brakl, F. Osseous Dystrophy Following Icterus Gravis Neonatorum, Arch. Dis. Childhood 14: 181-202, 1939.

[illegible] Sommerfeldt, F., and Brown, A. Osteodystrophia fibrosa, Am. J. Dis. Child. 57: 90-101, 1939.

[illegible] Docherty, M. B., Meyerding, H. W., and Wallace, G. T. Albright's Syndrome, Proc. Staff Meet. Mayo Clinic 19: 81-88, 1944.

[illegible] Oberndorfer, H. Die Simmondssche Krankheit, Med. Klin. [illegible], 1938.

[illegible] Marinesco, G., and Parhon, C. I. Sur un cas de diabète insipide avec cachexie hypophysaire, infantilisme, sénilisme, atrophie des organes génitaux et convulsions d' type épileptique, Rev. franç. d'endocrinol. 10: 105-146, 1932.

[illegible] Thannhauser, S. J. Werner's Syndrome (Progeria of the Adult) and Rothmund Syndrome, Ann. Int. Med. 23: 559-626, 1945.

[illegible] Turner, H. H. A Syndrome of Infantilism, Congenital Webbed Neck and Cubitus Valgus, Endocrinology 23: 566-574, 1938.

[illegible] Sharpey-Schafer, E. P. Pterygonuchal Infantilism (Turner's Syndrome) With Postmortem Findings, Lancet 2: 559-560, 1941.

ing and often contradictory endocrine symptoms although no definite relationship has evolved In *scleroderma* the most frequently observed and best founded systemic relationship is a disturbance of the *calcium* metabolism Thibierge and Weissenbach[1059] demonstrated calcium deposits in the sclerodermatic skin Later this observation was often confirmed[1060, 1061] but its significance denied again more recently[1062] The blood calcium and also the phosphorus were often found to be above normal[1063, 1066] and the tolerance to calcium expressed by the ability to restore the normal calcium level in the blood after injection of calcium was found disturbed[1067] Both calcium and phosphorus are retained in the body in scleroderma[1068] which is not in line with the negative calcium balance in hyperparathyroidism to which the relation seemed suggestive[1065] The Hamilton Schwartz *test for parathyroid hormone showed high values in the circulating* blood in two out of three cases of so-called *Werner's syndrome* (adult progeria) This syndrome is a rare heredo-familial disease in which scleroderma blue sclerae hypogonadism trophic ulcers metastatic calcification osteofibrosis and other endocrine stigmata are the main features.[1069-1070] The Hamilton Schwartz test was negative in two ordinary cases of scleroderma[1070] There is some evidence in support of hypoparathyroidism in scleroderma[1071] in the rare cases of its association with tetany

Primary atrophic and absorptive changes[1072, 1073] prior to the scleroderma in the *phalanges* and in the distal ends of other bones[1074] *osteomalacia*[1075-1076]

[1059] Thibierge and Weissenbach Concrétions calcaires sous-cutanées et sclérodermie Ann. de dermat et syph p 129 1911

[1060] Kennedy R L J Calcinosis and Scleroderma Treatment by Ketogenic Diet, J Pediat. 1 667-672 1932

[1061] Pautrier L. M Sclérodermies, chéloïdes et calcémie, Presse méd. 41: 345-347 1933.

[1062] Kaether H and Schaefer K. W Ca-Gehalt normaler Haut verglichen mit den Befunden bei Sklerodermie Klin Wchnschr 19: 333-334 1940.

[1063] Jung A and Hakki, A. C Études sur la calcémie Rev de chir 81 537-548 1933

[1064] Hillmann, H Beitrag zur Kenntnis der Sklerodermie Diss., Hamburg 1930.

[1065] Leriche R Jung, A., and DeBakey M. The Surgical Treatment of Scleroderma Sympathectomy and Parathyroidectomy 26 Cases, Surgery 1: 6, 1937

[1066] Cornbleet, T and Struck H C Calcium Metabolism in Scleroderma, Arch Dermat & Syph. 35 188, 1937

[1067] Rothman S and Weiss, I Calciumbelastungsproben bei Sklerodermie Klin Wchnschr 10: 1545-1546 1931

[1068] Barch, G E Scleroderma Symposium, New Orleans M & S J 92: 13-21 1939.

[1069] Oppenheimer B S and Kugel V H Werner Syndrome Am. J M Sc 202: 629-642 1941

[1070] Wiener N H The Hamilton-Schwartz Test and Hyperparathyroidism in Various Diseases, Am J M Sc 202: 642-650 1941

[1071] Simon H Sclérodermie et parathyroïdes, Gaz d. hôp. 108 875 1939

[1072] Bársony T and Frisch, E Beiträge zur Röntgenologie der Akroskleroze Fortschr d. Geb d Röntgenstrahlen 47: 297 303 1933

[1073] Leriche R and Jung A Nature et origine de la sclérodermie Bull Soc franç. d dermat. et syph 42 485-492 1935

[1074] Lebon J M Mereaux Fabregoule and Georges C cas de sclérodermie avec gros troubles de la calcification Rôle des parathyroïdes Bull et mém. Soc méd d Hôp de Paris 53 921-930, 1937

[1075] Marchiecka J Un cas de *maladie de Basedow associée à la sclérodermie* et à l'ostéomalacie Rev neurol 1 2 7 237 1929

[1076] Sterling W Der lipodystrophische und der osteomalacische Typus der gemischten sklerodermatischen Dystrophien Polska gaz lek 7 99-103, 1928 Zbl 27 181

bilateral cataract [illegible] the experimental production of scleroderma like skin changes in young rats and pigs following injection of parathormone[illegible] and finally the relatively successful *treatment of scleroderma* by unilateral *parathyroidectomy*[illegible] have given support to a *hyperparathyroid* etiology especially since some of the excised parathyroids were found hypertrophied or inflamed [illegible] However the results of parathyroidectomy are still controversial. [illegible]

There are many observations suggesting *other endocrine dysfunctions* Amenorrhea dysmenorrhea [illegible] onset of the disease in pregnancy and in the spontaneous and induced menopause [illegible] findings of ovarian changes the therapeutic success of estrogens, [illegible] and the 3 1 predominance of the female sex[illegible] are reasons enough to consider the *gonads* The situation is similar with regard to the pancreas thyroid [illegible] and pituitary It is now generally accepted that *acrosclerosis* [illegible] or sclerodactylia is essentially different from the diffuse or localized scleroderma (morphea) According to Sellei [illegible] *acrosclerosis is a vegetative neurosis* and is related to Raynaud's disease. True *scleroderma* however seems more likely to be a *fermentative* disorder related to the *pancreas* It has in some instances been successfully treated with pancreas liver stomach and duodenum extracts (Sellei[illegible] and many other articles by the same author)

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[illegible] Basch O R Lefhovici, R Durupt, A and Basch, M Sclérodermie vec concrétions calcaires syndrome d Thibierge-Weissenbach) associée à une atrophie cutanée Parathyroïdectomie Bull. et mém d hôp de Paris 50: 510-521 1934

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[illegible] Ban-Prusakov S Degenerativ oculo-sclerodermica, Warsz. Czas. lek. 2 127 1925 Zbl 18 876 1926

[illegible] Spitzer R Sklerodermie und Psoriasis bei Gravidität und Menstruation. Zbl. 17 370, 1925

[illegible] Vallette A Sclérodermie et pierres de la peau (Essai physiopathologique) Strasbourg méd (pt 2) 85 209-228, 1927 Zbl. 26 89

[illegible] Schorubef Sklerodermie, Zbl. 23: 612.

[illegible] Linser K Sklerodermie Zbl 34 657

[illegible] Harvier P and Lichtwitz, A.: Sklerodermie Zbl 30: 229 1929

[illegible] Weiss Sklerodermie-Sklerodaktylie Zbl 30: 447

[illegible] Mary A and Horowitz Treatment of Scleroderma With Ovarian Hormone and Autohemotherapy Bull Soc franç de dermat. et syph. 41 64-71 1934 Abst., Dermat Ztschr 70 1 1 1934.

[illegible] Kornmann, S and Urbanner St. Sclerodermie Dansk. d. II Ok. 8, 3 717-803 1931

[illegible] Rothman, S Endokrine Störungen bei Sklerodermie Klin. Wchnschr 4 1091 1925

[illegible] Sellei, J Sklerodaktylie progressive Sklerodermie (Akrosklerose) Dermat Ztschr 64 131-146, 1932.

ing and often contradictory endocrine symptoms although no definite relationship has evolved. In *scleroderma* the most frequently observed and best founded systemic relationship is a disturbance of the *calcium* metabolism. Thibierge and Weissenbach[1] demonstrated calcium deposits in the sclerodermatic skin. Later this observation was often confirmed[2,3] but its significance denied again more recently.[4] The blood calcium and also the phosphorus were often found to be above normal[5,6] and the tolerance to calcium, expressed by the ability to restore the normal calcium level in the blood after injection of calcium, was found disturbed.[7] Both calcium and phosphorus are retained in the body in scleroderma,[8] which is not in line with the negative calcium balance in hyperparathyroidism, which the relation seemed suggestive.[9] The Hamilton-Schwartz test for parathyroid hormone showed high values in the circulating blood in two out of three cases of so-called *Werner's syndrome* (adult progeria). This syndrome is a rare hereditary familial disease in which scleroderma, blue sclerae, hypogonadism, trophic ulcers, metastatic calcification, osteofibrosis and other endocrine stigmata are the main features.[10,11] The Hamilton-Schwartz test was negative in two ordinary cases of scleroderma. There is some evidence in support of hypoparathyroidism in scleroderma[12,13] in the rare cases of its association with tetany.

Frequently atrophic and absorptive changes[14,15] prior to the scleroderma in the *phalanges* and in the distal ends of other bones, *osteomalacia*[16,17]

[1]Thibierge and Weissenbach: ... calcaires sous-cutanées ... sclérodermie ... dermat. et syph. ... 1911.

[2]Kennard, ... Calcinosis and Scleroderma: Treatment by Ketogenic Diet. J. Pediat. ... 667-673, 1932.

Pa... ... Sclérodermies, ... et calcinose, Presse méd. 41: 345-347, 1933.

Kaether ... and Schaefer ... Erhalt normaler ... verglichen mit den Befunden bei Sklerodermie. Klin. Wchnschr. ... 1930.

... and Hakki ... Études sur la calcémie. Rev. de chir. ... 1932.

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Oppenheimer, B. ... and Kugel, V. H.: Werner's Syndrome. Am. J. M. Sc. 202: ... 1941.

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Maranon, ... Sclérodermie et para... Bull. et mém. Soc. méd. d. hôp. ... 1929.

[?]... and Erbeck ... Beitrag zur Ätiologie der Akrosklerose. Fortschr. ... Röntgenstrahlen ... 1933.

[?]Leriche, R. and ... Nature et origine de la sclérodermie. Bull. Soc. franç. de dermat. et syph. ... 1933.

[?]... Hérédité et ... sclérodermie ... troubles de calcification. Bull. et mém. Soc. méd. d. hôp. de Paris ... 1937.

[?]... de maladie de ... sclérodermie et à l'ostéomalacie. Rev. neurol. ...

[?]Sterling, W.: Der ... atrophische und der osteomalacische Typus der ... sklerodermatischen Degeneration ... 1925 ...

Among the many endocrine symptoms which have been reported in connection with the rare *poikiloderma atrophicans vasculare* the relatively frequent onset in the *menopause* seems worthy of mention.[1776] The same is true of *acrodermatitis atrophicans*. In this dermatosis which is not very rare in some parts of Europe the females outnumber the males 2:1.[1882] There are some observations of acrodermatitis atrophicans in Graves' disease.[1883]

Acrocyanosis.—*Erythema venosum*,[1884] *Erythrocyanosis symmetrica*,[1885] *Erythrocyanose symmétrique malléolaire des jeune filles*.

Symmetrical sometimes circular palm-sized cyanotic plaques almost exclusively occurring in young girls[1886] have been described under several names.[1887] The plaques are mostly seen anteriorly or laterally on the lower legs, less often on the inner aspects of the thighs right above the knees. The lesions are bluish red sometimes with bright red (cinnabar) spots[1888] and some thin telangiectases. The erythema vanishes on pressure. The skin is taut and cannot be folded. The lanugo has usually disappeared. There is an ill-defined deep firmness which gives a doughy impression though there is no pitting. The lesions are cooler to the touch than the normal skin. Superficial ulceration has been seen but this is rare.[1889,1890] Local fat increase has been described.[1891] There is only minimal nonspecific inflammation around the vessels. Capillaroscopy reveals varicosities of the capillary veins and frequent spasms.[1892] The course is an extremely chronic one. The lesions appear in the winter time, improve in summer to some extent and reappear with the first frost. Like many lower leg conditions they are better after a night's rest and worse again in the evening. The dermatosis is clinically closely related to chilblains from which it differs in the site and the accompanying circumstances which make an ovarian relation probable.[1893] The patients are overwhelmingly *young girls* and women up to about thirty years of age.

Children do not seem to become affected though they are very susceptible to chilblains. Irregularities of menstruation,[1894] obesity[1895] and other endocrine

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[1882]Jessner, M., and Löwenstamm, A. Bericht über 66 Fälle von Akrodermatitis chronica atrophicans, Dermat. Wchnschr. 79: 1169, 1924.

[1883]Beneny, R. and Bertin, E. Ätiologie der Acrodermatitis atrophicans Herxheimer. Klin. Wchnschr. 12: 276-277, 1933.

[1884]Beardman, W. P. Scleroderma. Arch. Dermat. & Syph. 19: 901-916, 1929.

[1885]Ochsner, A., and DeBakey, M. Peripheral Vascular Disease. Treatment. Surg., Gynec. & Obst. 70: 1058-1072, 1940.

[1886]Ochsner, A. and DeBakey, M. Scleroderma, New Orleans M. & S. J. 92: 13-24, 1939.

[1887]Lengfellner. Erythema venosum, München. Med. Wchnschr. 67: 962, 1920.

[1888]Bel, P. Erythrocyanosis cutis symmetrica, Klin. Wchnschr. 1: 578-580, 1922.

[1889]Ullmo, A. Érythro-cyanose symétrique sus-malléolaire des jeunes filles, Thèse de Strasbourg, 1929.

[1890]Nicolas, J. and Petouraud, Ch. Érythro-cyanose symétrique sus-malléolaire des jeunes filles. Nouvelle pratique dermatologique, Vol. 6, Paris, 1936, Masson & Cie, pp. 389-393.

[1891]Lortat-Jacob, Solente, G. and le Baron. Érythro-cyanose des membres inférieurs. Présence de taches cinabres. Leur provocation réflexe. Bull. Soc. franç. de dermat. et syph. 38: 1290-1291, 1931.

[1892]Baer, T. Stauungsdermatosen. Ibid. 43: 603.

[1893]Cardelli, L. Contributo alla conoscenza dei fenomeni di eritrocianosi degli arti inferiori, Gior. ital. di dermat. e. sif. 69: 81, 1929.

[1894]Kreibig. Akrocyanosis cruris. Ibid. 33: 416, 1930.

[1895]Seibel and Lieberr. Erythrocyanosis extremitatis chronica, Arch. f. Dermat. u. Syph. 180: 277, 1939.

stigmata like hyperidrosis of palms and soles. Marañon's[illegible] main hypogenitalism, dry skin, goiter[illegible] and adrenal hypertension[illegible] have often been observed.[illegible] The condition has also been seen after castration.[illegible] Estrogen therapy and thyroid have been helpful in many cases. Yet no entirely convincing endocrine relationship has so far been established. Tuberculosis[illegible] has been considered since some cases developed into tuberculosis indurativa.[illegible] The condition seems to be rarer in the United States than in the corresponding climates in Europe.

[illegible] Marañon, G.: The Hypogenital Hand. Acrocyanosis. [illegible] 472-475, 1931. [illegible]

[illegible] Thomas, E.: [illegible] la période [illegible] 1931. [illegible]

[illegible] J.: L'acrocyanose permanente des jeunes sujets. Arch. de méd. d. enf. [illegible] 1929. [illegible]

[illegible] Galant, J. [illegible] Hyperacrohidrosis. Virchows Arch. f. path. Anat. 267: [illegible] 1928.

[illegible] Villaret, M. and [illegible] L'acrocyanose des jeunes femmes. Importance physiopathologique et pathogénique de l'hypertension [illegible] et de l'insuffisance ovarienne. Arch. d. méd. d. enf. [illegible] 1929. [illegible]

[illegible] Feller, M.: Menstruelle Dermatosen. Derm. Ztsch. [illegible] 1928.

[illegible] Juster, E.: Les [illegible] des [illegible] hypothyroïdiques [illegible] Bull. Soc. franç. de derm. et syph. [illegible] 1929.

[illegible] Casazza, R. and [illegible] J.: [illegible] Giorn. ital. di derm. e sif. 73: [illegible] 1932.

CHAPTER XXVII

AGEING*

Senile *atrophy* of the skin starts shortly after the age of forty[1985] The epidermis becomes thinner at the expense of the lower strata. The horny layer appears looser The mitoses in the basal layer become scarcer or disappear completely and the cells of the basal and prickle cell layers show perinuclear vacuolization The stratum granulosum is hardly discernible.[1986] The papillae flatten and lose their elastic fibers The collagenous fibers grow thinner and stain poorly The elastic fibers show clumping shortening thickening and irregular positions together with marked hyperplasia especially in the face and neck. This hyperplasia of the elastic tissue may account for the yellowish tinge of the face and hands in some old people[1986]

Elacin collastin and collatin are often present.[1987] The peculiar accumulations of elastic fibers in the facial skin known as elastica mimica[1986] which develop at puberty and reach their highest development at thirty are definitely regressive at forty At sixty the alterations of the elastica are marked[1988] The elastic fibers of the blood vessels especially of the elastica interna, participate in the changes. The senile changes in the elastic fibers seem to depend on exposure to light and elements, since they were not found in unexposed skin of old people[1989]

Extravasation on slight trauma (*purpura senilis*) is common

Severe arteriosclerotic changes may be observed along with corresponding senile changes in other organs.

The *sebaceous glands* are reduced in number and they show certain qualitative changes. In the face especially on the nose and forehead hyperplasia of the sebaceous glands is common after the age of forty The hair follicles are often found without hair and the musculi arrectores pilorum are usually atrophic. The subcutaneous fat shows degeneration[1987] The water content of the senile skin is reduced[1989-1990] and the rate of insensible perspiration is lower than in young subjects.[1991] The capillary reactivity to mechanical and other stimuli

*See table at the end of the book.

[1985] Evans, R Cowdry E. V and Nielson, P E Ageing of Human Skin Influence of Dermal Shrinkage on Appearance of Epidermis in Young and Old Fixed Tissues, Anat. Rec. 86 545-565, 1943.

[1986] Cowdry E V editor Problems of Ageing, ed 2, Baltimore 1942, Williams and Wilkins Co. Chapter on Skin by F D Weidman.

[1987] Kasorla M Changes in the Senile Skin, Ukrain med Arch 6 1-8, 61 100, 1930 Zbl 48 640

[1988] Ejiri, I Differences i the Elastic Fibers of the Skin According to Sex and Age, Jap J Dermat. & Urol 40 210, 2 7 1936 Abstr Arch. Dermat 37 664, 1938.

[1989] Hill, W R and Montgomery H Regional Changes and Changes Caused by Age in Normal Skin, J Invest Dermat 3 23 241, 1940.

[1990] Bürger M and Schlomka, O Chemische Gewebsuntersuchung für die Altersforschung, Klin Wchnschr 7 1944-1948, 1929.

[1991] Burch, G E Cohn, A E and Neumann, C. Ra of Water Loss From Finger Tips and Toe Tips in Normals, Seniles, etc Am. Heart J 23 185-196, 1942.

is slow in response and slow in return to the normal status.[19, 1941] Cavallucci who systematically studied the *physiological reactions* of the senile skin in comparison with that of the middle aged found red dermographism delayed and urticaria factitia less frequent and less pronounced. Marañon's sign (see thyroid), the pilomotor reaction and the urticarial intracutaneous morphine reaction are also less marked. Senile atrophy causes decrease of the sensitivity to touch, pain and temperature. The fact that old people suffer from cold more than young persons is not due to increased sensitivity but to other, probably vascular factors.



Fig. [illegible]. Purpura senilis.

The cutaneous manifestations of ageing are of practical importance for the *objective determination* of the age.[1943, 1944] At the age of 20 the facial skin is still free of wrinkles. The cheeks are rounded so that the mouth and nose appear small. At 25 the forehead and the lower lid show the first wrinkles and the nasolabial folds become apparent. The veins of the back of the hand begin to show.[843] At 30 crow's feet appear at the lateral angles of the eyes. The beard growth is most vigorous between 30 and 40. At this age men often become more hairy on the chest, arms, and the dorsa of the hands. The occipital hairline loses its sharpness.

The thirty fifth year usually marks the first folds in front of the ears. (Nudeshdin after Sebastiany[1944].) These preauricular wrinkles increase in length more than in depth so that some criminologists have attributed much importance just to the length of these folds.[1944] Graying of the hair at the temples and a less

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[1940] Bettmann, S. Altersveränderungen im Gefässendabschnitt der Lippenschleimhaut. Ztschr. f. Anat. u. Entwicklungsgesch. 93: 460-477, 1930. Zbl. 371:600.

[1941] Cavallucci, U. Anatomia, fisiopatologia della cute. Reattività della cute senile. Gior. ital. di dermat. e sif. 75: 678-679, 1934.

[1944] Sebastiany, V. Ueber objektive Altersschätzung am lebenden Erwachsenen. Diss. Bonn, 1927.

[843] Müller, L. R. Altersschätzung des Menschen. Berlin, 1922. Julius Springer.

rosy and more ruddy hue of the cheeks may become noticeable in the fourth decade The age of graying varies widely A familial factor can often be recognized.

A person of 40 already has most of the typical wrinkles. The preauricular wrinkles are now multiple and extend upward to the upper level of the tragus. The cervical folds, which run from the chin down to the jugulum may be seen in lateral light.

At 45 the suborbital wrinkles become more marked. In light coming from the side the cervical folds can now be clearly seen . The lips start to become thinner In a fat person the double chin is marked and in a lean person the cervical skin becomes too wide The eyebrows may become bushy or at least a few long hairs may grow





Fig 224. Fig 225

Fig. 224.—Female aged 63 years. Long ear preauricular wrinkles

Fig. 225.—Cervical and other folds and wrinkles.

In the early fifties all the wrinkles grow deeper The hands become wrinkled. Small wrinkles of the bridge of the nose of the ear lobe and of the chin are present. The entire skin is now relatively dry The graying of the hair can no longer be concealed by pulling out of the white hairs.

Senile hyperpigmentation starts around 55 Wrinkles on the bridge of the nose, the ear lobes and the chin become marked The longitudinal cervical folds are accented. The rhomboidal crossing folds in the nape of the neck (Cutis rhomboidalis) are seen in some men especially those who live an outdoor life

In the sixth decade the teeth appear to be longer because of atrophy of the alveolar ridge.

At 60 the first radial wrinkles around the mouth appear on the upper lip. The cheeks become loose and droopy. The glans penis becomes smaller and the penile skin wrinkled and darker. The pubic hair in the male appears thin and less curly, though possibly spread over a wider area than in younger years. The scrotum is longer and more flaccid and fails to contract on exposure to cold, probably because of atrophy of the tunica dartos.



Fig. 236



Fig. 237

Fig. 236. Male aged 7 years. Long ear, droopy eyelids, preauricular fold. Pigmented spot.
Fig. 237. Vermilion of lips has disappeared. Wrinkles cross lips.

In the female analogous regression of the labia majora takes place. The subcutaneous fat is often accumulated around the hips, leaving the extremities and the chest relatively lean. The formation of the arcus senilis corneae begins.

Around 65 the hair growth in the ear ducts, the nostrils and on the nape of the neck becomes more conspicuous in men as well as in women. The brittle hypertrichosis on the chin is often marked in the female sex.

At the age of 70 the facial wrinkles are often found crossing each other. Sometimes they form a netlike pattern, or a papyraceous wrinkling like that seen in castrates. Senile pigmentations have increased. The skin is thin and a fold lifted from the back of the hand returns but slowly to the normal position. The head hair is usually thin or has disappeared. Complete senile baldness is occasionally seen in women also.



Fig. [illegible].—Female aged 80 years. All wrinkles are developed. Drooping upper lid. Vermilion of the lips has disappeared.



Fig. [illegible]. Male aged 78 years. Senile atrophy of the skin.



Fig. 240.—Female aged 63 years. Senile keratoma; basal cell epithelioma of nasolabial fold. Crossing wrinkles around the mouth. Vermilion border has disappeared.



Fig. 241.—Male aged 88 years. The long ear of old age.

The thinning of the lips is completed at 75 so that hardly any vermilion can be seen. The thin mouth appears longer and sunken because of the atrophy of the alveolar ridges and the loss of the teeth The backs of the hands are wrinkled like thin paper



Fig 242 — Male aged 73 years Loose teeth of old age



Fig 243 —Senile pigmented spot

The eighties are characterized by the tired expression of the eyes caused by the drooping upper lid (senile ptosis) The radial wrinkles around the mouth are conspicuous The cervical folds which appeared long before are very marked. The ears not only appear longer but are actually larger and flabby The nose



Fig. [illegible].—Senile keratoma.



Fig. 215.—Senile hemangioma of the vermilion border.

seems to be larger The skin of the back of the hands is now very yellowish thin and pigmented and the underlying fat has practically disappeared The muscles have atrophied. The knuckles and small joints are very marked There are not only transverse wrinkles but also longitudinal folds. The hand gives a bony impression

It should be kept in mind that all signs of ageing are subject to relatively wide variations. However the evaluation of the appearance of wrinkles is a fairly reliable guide to objective age estimation

Old age predisposes to a great number of *dermatoses* Epitheliomas keratoses pigmented spots small hemangiomas, especially the hemangioma of the vermilion border of the lips, xanthelasmas of the eyelids sebaceous adenomas pendulous fibromas (acrochordon) and other neoplasms are common The dryness of the skin caused by the reduction of the sebaceous glands is often troublesome. Pruritus senilis is another common and stubborn skin trouble of old age probably caused by the vascular changes. Purpura senilis (Bateman after Pasini[illegible]) is found on the acral and extensor surfaces. On slight trauma or even without it telangiectatic and purpuric spots appear and undergo the usual color changes leaving long lasting pigmentations Such spots are often found on the back of the hands where the senile atrophy is pronounced and the exposure to slight trauma is greater than of other parts. Purpura senilis does not disturb the well being of the patient

Thickening and opacity or dark discoloration of the toe nails is a common sight in old people The rate of growth of the hair and of the nails is substantially reduced [illegible]

[illegible] Pasini, A Purpura Senilis, Monatsh f prakt. Dermat 42 43 1906

Chapter XXXIII

METABOLIC DISORDERS

Diabetes

The Blood Sugar Test.—With the increasing knowledge of diabetes, particularly with the development of the methods of blood sugar determination a large number of investigators have studied dermatoses in hyperglycemia as well as the presence of hyperglycemia in dermatoses. Today it is generally held that the absence of sugar in the urine does not rule out diabetes. The determination of the blood-sugar level after fasting and after a measured intake of sugar has become an important diagnostic procedure and many investigators have tried to correlate dermatoses and the blood sugar.

The normal fasting values given by different authors vary considerably but 80 to 120 mg. in 100 c.c. of blood may be considered normal. The gravimetric method (Bang, Hagedorn and Jensen) give lower values than the colorimetric method (Folin and Wu). Population with a diet rich in carbohydrates have a higher average blood sugar level than groups whose carbohydrate is lower.[illegible] For the determination of sugar tolerance some authors prefer the intravenous injection of glucose to the oral administration, but today the drinking of 100 grams of dextrose in water after twelve hours of fasting and the determination of the blood sugar after one-half, one, two and three hours is a standard method.[illegible] It not only avoids the intravenous injection but duplicates the normal manner of sugar intake. It must be emphasized that disorders of the endocrine-sympathetic system, menstruation, exertion during the test and under- or overfeeding with carbohydrate during the days before the test may influence the blood sugar curve. Urbach considers a blood sugar tolerance curve characteristic for diabetes only if

(1) The highest point of the curve is reached later than one-half hour after the ingestion of the sugar.
(2) If the course of the curve is protracted enough to form a flat curve instead of the normal steep type.
(3) If the fasting value has not been reached again within three hours.

Blotner[illegible] considers potential diabetes if the peak of the curve reaches 165 mg. per cent in one-half or one hour and he diagnoses diabetes when the blood sugar exceeds 170 mg. and some or all of the urine specimens contain sugar.

Carbohydrate Metabolism in the Skin.—Urbach and his collaborators designed a method of examining the skin sugar content which requires only a

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[illegible] Urbach, E.: Beiträge zu einer physiologischen und pathologischen Chemie der Haut. Isolierte kutane Glykohistechie als Ursache chronischer Dermatosen, Med. Klin. 29: 230-240, 1933.

[illegible] Blotner, H.: Glycosuria and Diabetes Mellitus in Selectees, J.A.M.A. 131: 1109-1114, 1946.

very small quantity (30 to 40 mg.) of skin taken with an electric biopsy punch of 3-5 mm.[1048,1049]

The skin sugar content in laboratory animals varies considerably. In the rabbit it reaches 143 per cent of the blood sugar, the highest of the known values. The normal human fasting skin sugar amounts to only 58 per cent of the blood sugar.[1049] These findings are remarkable because the blood sugar levels in man and in laboratory animals do not differ greatly, both being between 83 to 111 mg. per cent. These figures refer to the so-called free sugar. The bound sugar which can be obtained only by acid hydrolysis is fifteen times higher. The skin makes up 16 per cent of the body weight. Only the muscles weigh more of all the organs. Considering the high sugar content, together with the fact that the skin weighs one-sixth of the body and three times more than the liver, it is apparent that the skin is likely to be important in the sugar metabolism. Urbach[1047] considers a fasting skin sugar level of more than 68 mg. per cent as pathologic. He showed that the curve obtained by skin sugar determinations after oral administration of 100 grams of dextrose imitates the blood sugar curve, but it requires about one-half hour more to reach the maximum and about one hour more to reach the fasting value again. Diet low in carbohydrate preceding the test causes a lower fasting level of the skin and blood sugar and a much higher maximum level of the skin and blood sugar curves than a high carbohydrate diet. A diet high in fat lowers the sugar content of the skin while the blood sugar level remains the same.[1049] In the depancreatized dog the skin sugar increases much more than the blood sugar.

In diabetics the $\frac{\text{skin sugar}}{\text{blood sugar}}$ ratio is high. Following the tolerance test the skin sugar is almost doubled and the time required for return to normal may be longer than five hours.[illegible] This demonstrates that the diabetic skin stores sugar for a long time and would explain its often observed susceptibility to infections. Storage, decomposition and excretion of sugar seems to be a normal function of the skin.[991]

Urbach found in diabetics with dermatoses such as furunculosis, hydradenitis, eczema, urticaria and pruritus the skin sugar higher (85 mg. per cent) than in diabetics without dermadromes (66 mg. per cent) in spite of about equal blood sugar levels. Thus in the diabetics with dermadromes the ratio $\frac{\text{skin sugar}}{\text{blood sugar}}$ seems to be higher than in those without dermadromes. In animals poisoned with extremely high doses of insulin the skin sugar never fell below a certain level. In diabetic patients, diet and insulin could not lower the skin sugar below 39 mg. per cent. Pillsbury[1050] made the existence of an autonomous carbohydrate metabolism in the skin still more evident by studying lactic acid

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[1048] Urbach & Fantl. Der Zuckergehalt der normalen Haut. Biochem. Ztschr. 196: 474, 1928.
[1049] Urbach, E. and Lentz, J. W. Carbohydrate Metabolism and the Skin. Arch. Dermat. & Syph. 52: 301-316, 1945.
[991] Folin, O., Trimble, H. C. and Newman, L. H. The Distribution and Recovery of Glucose Injected into Animals. J. Biol. Chem. 75: 263-281, 1927.
[1050] Pillsbury, D. M. The Intrinsic Carbohydrate Metabolism of the Skin. J.A.M.A. 96: 426-432, 1931.

formation in the skin He found this characteristic product of carbohydrate metabolism to be normally present The skin contains several enzymes concerned with the splitting of carbohydrates The stages of this process are the same as in the muscle and in the liver[183]

Urbach and his associates[184,185,186,187] discovered what they called *isolated skin diabetes* or cutaneous glycohistechia They found that there exist in some cases a high fasting skin sugar and a flattened skin sugar tolerance curve in the presence of normal fasting blood sugar and a normal blood sugar tolerance curve The patients suffered mostly from chronic eczema furunculosis and vaginal or anal pruritus A certain number of them responded well to insulin and a diet low in carbohydrates clinically as well as in the fasting skin sugar and in the skin sugar tolerance curve No transition of skin diabetes into frank diabetes has been observed[18] This skin diabetes has not become widely known mainly because of the necessary punch biopsies and the new analytic method



Fig 31 Skin diabetes with eczema (Urbach) (From Urbach, E Skin Diseases, Nutrition and Metabolism Grune & Stratton, Inc)

Besides the excised skin sweat and serum from artificial blebs have been studied with regard to their sugar content Urbach emphasizes that the analysis of bleb serum is no substitute for that of skin tissue The blister serum sugar is higher than the skin sugar Its changes after sugar ingestion are similar but

[183]Wohlgemuth, J Ueber den Kohlehydratstoffwechsel der Haut Deutsche med Wchnschr 57 1814-1815, 1931

[184]Moncorps, C Kohlehydratstoffwechsel und Haut Jahresk f ärztl Fortbild 22 27-36 1931

[185]Urbach, E Isolierte Glykohistechie als Ursache chronischer Furunkulose Zbl 41 802, 1932.

[186]Urbach, E Depisch, F and Fisher O Isolierter hoher Hautzucker bzw Hautdiabetes, Klin. Wchnschr 16 442, 1937

[187]Urbach, E Skin Diabetes, J.A M.A 129 438-440, 1945.

slower than those of the blood sugar [illegible] In persons who are intolerant to sugar the sweat contains an abnormal amount of sugar After ingestion of much dextrose the sweat sugar may increase 100 to 150 per cent or more even 300 to 400 per cent. [illegible] The sugar from evaporated sweat may accumulate on the skin and cause irritation pruritus and folliculitis just as the sugar does in persons who are occupationally in contact with sugar Carrié and Koenig[illegible] measured the sugar accumulated on the skin It reaches its maximum four days after a bath the armpits collecting more sugar than open areas. The sugar on the skin is much higher in diabetics than in normal persons. The sweat sugar values determined by reduction only have been considered more recently as being much too high [illegible]

Another approach for testing the skin in diabetes has been advanced by Seelig [illegible] Using the method of McClure and Aldrich he compared the time which a wheal produced with .5 c c of 1 per cent aqueous glucose solution needed to disappear compared with one produced with 9 per cent saline solution. In diabetics and glucose wheals disappeared more quickly yet never before the controls with saline wheals. This seems to indicate an increased avidity of the diabetic skin for glucose

The majority of the investigators tried to find out how the blood sugar influences the skin The possibility that the *skin* or at least pathological changes of the skin might *influence the blood sugar* has been given much less attention

Skin irritations of many kinds e g from croton oil [illegible] injections of saline foreign proteins and olive oil increase the blood sugar within certain limits according to the intensity of the inflammation. [illegible] The extract of artificially inflamed skin injected into normal rabbits raises the blood sugar level to a larger extent than extracts of normal skin The increase is higher in rabbits with already inflamed skin than in rabbits with normal skin It is interesting that high blood sugar curves in psoriasis may become normal after the skin symptoms have been cleared by local treatment. [illegible] Marchionini and

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[illegible] Ferrari, A. V Raffronti fra il contenuto in glucosio del sangue del liquido di bolle dopo la somministrazione di saccharo per via orale ad individui normali, Dermosifilografo [illegible] 1931 Zbl. [illegible] 763.

[illegible] Bronzini, M La funzione renale in alcuni dermopazienti, Arch Ital. di. dermat [illegible], 1931 Zbl [illegible] 764.

[illegible] Usher B and Rabinowitz, I M. Excretion of Sugar in Sweat, Arch. Dermat. & Syph [illegible] 706-712, 1927

[illegible] Carrié C and Koenig, H Ueber den Zuckergehalt auf der Haut bei Normalen und Diabetikern, Arch f Dermat Syph. [illegible] 611-614, 1936.

[illegible] Scholtz W Sugar Content of Skin and Sweat. Comparative Study of Diabetic and Nondiabetic Subjects Arch f Dermat Syph [illegible] 471-[illegible], 1940.

[illegible] Seelig, S F Diabetes Diagnosis, Intradermal Skin Tests, Guy Hosp Rep. [illegible] 210-217 [illegible].

[illegible] Thiemann, L Effect of Irradiation With Monochromatic Light on Blood Sugar and Lactic Acid in Rabbit Biochem Ztschr [illegible], 1934

[illegible] Ayres S J Glucose Tolerance Reactions in Eczema, Arch Dermat & Syph [illegible], 1935

[illegible] Yarahara A Experimental Studies on Skin Sugar Jap J Dermat & Urol. [illegible] 113-1128 1930 [illegible] 87 101 1932 [illegible] 1933 240-300 1933 Zbl [illegible] 764 [illegible] 181 [illegible] 811

[illegible] Miyake I Einfluss von Dermatitis—Hautentzündung auf Blutzucker Jap J Dermat & Urol. [illegible] 1300-1322, 1931 Zbl [illegible]

[illegible] Marchionini, A and Ottenberg, K Ultraviolettbestrahlung und Kohlehydratstoffwechsel Klin. Wchnschr [illegible] 1307 1309, 1933.

[illegible] Mascerpa, O Bohnstedt, R M and Schmid, R. Sugar and Glutathion Content of Skin, Arch f Dermat. u. Syph. [illegible] 67 78, 1933.

Hövelborn[175] studied the influence of ultraviolet light on the carbohydrate metabolism. At the height of the erythema the fasting value of the blood sugar drops and the blood pressure decreases. This, together with the increase of blood diastase, points to one or several insulin resembling[1,4] substances in the skin, produced either in the skin or in the pancreas on stimulation from the skin. Moncorps[176] also found a substance in the skin which raises the blood sugar.

Incidence of Dermatoses in Large Groups of Diabetics.—Greenwood[177] compared the skin of 500 diabetic and 500 nondiabetic general hospital patients. About 25 per cent of the diabetics either had or had had skin diseases, mainly pruritus (7 per cent), eczema, epidermophytosis, furunculosis and carbuncle (2 per cent), and xanthoma palpebrarum (18 per cent). The patients with a dry skin (20 per cent) seemed to be more apt to develop dermatoses than those with a moist skin. The figures were generally higher than in the nondiabetic group. The total percentages in the control group are meaningless because of the difficulty to obtain reliable figures for epidermophytosis. Tauber[178] found among 514 diabetics, most of whom were hospital patients, gangrene in 18 per cent, ulcers in 4.3 per cent, furuncles and carbuncles in 3.8 per cent, infected hands and feet in 23 per cent and pruritus vulvae et ani in 0.8 per cent. This and other lists show that the recorded incidences vary widely even in large groups, probably due to the selection of the studied series. Statistics of hospitalized diabetics are apt to carry a high percentage of severe complications, especially gangrene, which are much rarer in ambulatory groups (Lane's series given in Greenwood[177]).

How often is a dermatosis the presenting symptom of diabetes? Every experienced dermatologist will remember with satisfaction the cases of perioral eczema, balanitis or pruritus in which he first made the diagnosis of an underlying diabetes. In the large material of the Berlin University Skin Clinic 27 out of 1,000 patients were diabetics and only 13 per cent of them knew of their disease. In the others their diabetes was diagnosed by the dermatologist. Among the diabetic skin patients of the Berlin Clinic 59 per cent had eczema (one-fifth of these eczema of the genital region) and 22 per cent balanitis. These patients represent a group with uncontrolled diabetes.

The degree of control of the diabetes is probably the main factor which influences the incidence of dermadromes. The whole dermatological aspect of diabetes has changed since the introduction of insulin. In examining about 200 diabetic patients, most of whom were well controlled, the author was surprised to see how rare were even those skin diseases which are generally considered typical of diabetics. Epidermophytosis was seen to be neither more common nor more severe than in nondiabetics. Gangrene, furunculosis and carbuncle were rare, about 1 per cent. The most common skin change in the controlled diabetic is a slight yellow discoloration, probably due to minor degrees of carotenemia (Xanthosis diabeticorum).

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[177]Greenwood, A. M.: Skin in Diabetes. 500 Cases. J. A. M. A. 89: 774-776, 1927.

[178]Tauber, E. B.: Hyperglycemia in Diseases of the Skin. Arch. Dermat. & Syph. 27: 189-205, 1933.

Mycoses.—Greenwood[1776] found epidermophytosis in 40 per cent of his series of 500 diabetics. Greenwood and Rockwood [1776] found clinical evidence of fungus infection in the interdigital spaces of the feet in 70 per cent of diabetic patients their diabetes being generally uncontrolled All thickened and opaque



Fig. 247 — Epidermophytosis in diabetic patient.

nails were found to be infected No relationship to the blood sugar level could be established. Percentages of other authors vary widely (see table in Gray and Close.[1777]) Because of the great differences in the incidence in normal control groups it is difficult to state whether the incidence in diabetics is actually higher than in comparable normal groups. Many authors [1778] emphasize the importance of the nails as a source of reinfection.

The importance of *mycotic foot infections* in diabetics lies in the danger of more severe infections complications and gangrene The clinical aspect of epidermophytosis in diabetics does not seem to have special features.

Every dermatologist has seen in obese women the characteristic, though not very common picture of intertriginous genito-inguinal and inframammary dermatitis often caused by *monilia* This bright red sharply bordered intertrigo surrounded by small pustular satellites is very suggestive of diabetes Oral moniliasis (thrush) is common in infants but is rare in adults. If it occurs urine

[1776] Greenwood, A. M and Rockwood, E. M Skin in Diabetic Patients, Arch Dermat & Syph. 21 96-107 1930

[1777] Gray H and Close W E Chiropody and Diabetes, M Rec. 154 445-449, 1941.

[1778] Kelly H J Significance of Dermatophytosis (Cause of Gangrene) Pennsylvania M. J 41 441-446, 1938.



Fig. 21 [illegible] diabetic. Intertriginous monilia infection of the groin.



Fig. [illegible] [illegible] diabetic. Inframammary moniliasis.



Fig. 230. Inframammary moniliasis in obese diabetic woman aged 50 years



Fig. 231.—Erosio interdigitalis in diabetic woman.

and blood should be examined for sugar.[175] Yeast infections of the hands, feet and particularly of the vulva occur mostly in uncontrolled diabetics.[176] Proper management of the diabetes without local treatment can control the infection. This indicates the specific influence of the diabetes.



Fig. 132. Moniliasis in diabetes. (Courtesy Dr. [illegible] of Dermatology, Department of Medicine, University of Chicago.)

Diabetic vulvovaginitis is usually a mycotic infection.[177, 178] It is encountered in about 50 per cent of women with diabetes. The vulva appears slightly swollen and tender, with a reddish blue color and a thin grayish surface. Abrasions and excoriations, together with a sensation of heat, cause much discomfort. The inflammation is usually limited to the moist surfaces but may extend to the mons

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[175] Christoph: Foot and Diabetes, Zbl. 22: 606, 1927.

[176] Traut, H. F., Whit[illegible], L., and Hemphill, R. B.: Moniliasis of the Skin in Diabetes, J. A. M. A. 103: 1290-1292, 1934.

[177] Hesseltine, H. C.: Diabetic or Mycotic Vulvovaginitis, J. A. M. A. 100: 177-178, 1933.

[178] Hesseltine and Campbell: Diabetic or Mycotic Vulvovaginitis, Am. J. Obst. & Gynec. 35: 272-283, 1938.

veneris, anus and crural folds Small white areas (thrush spots) on the labia minora contain yeasts. Glucose applied in powder or solution is supposed to cause a flaring up of the vulvitis in mycotic infections as compared with vulvitis of other causes. Hesseltine[1977] speaks of mycotic vulvitis rather than of diabetic vulvitis, because it is not the irritation from the sugar-containing urine but the infection that causes the vulvitis The sugar fermenting yeast, of course finds a good medium in the glucose-containing urine and tissues. Optimal growth of yeasts and also of staphylococci, is found on media with 150 to 200 mg per cent of sugar This figure corresponds well to the sugar contents of serum in many diabetics[1978]

Diabetes was the cause in 26 of 31 consecutive patients with pruritus vulvae[1979] Fifteen of these 26 diabetics failed to show sugar in the urine Only blood sugar tests and a detailed history established the diagnosis. These women were between thirty and fifty years of age Such cases may often be treated as menopausal pruritus if no finer diagnostic test than the unreliable urine test is used



Fig 181.—Diabetic balanitis and ulcer of glans penis. (From Urbach, E Skin Diseases, Nutrition and Metabolism, Grune & Stratton, Inc)

Diabetic *balanitis* is much rarer than vulvitis the ratio being 1:3 [1980] It occurs less often in circumcised men whose glans penis is dry and does not give the yeasts such a favorable moist medium. Among 147 cases of diabetic balanitis treated in the University Skin Clinic in Berlin there was not one in a circumcised man

Eczema surrounding any not only the urethral and anal orifices is always suggestive of diabetes. Eczema around the eyes may be caused by sugar-containing tears, perioral eczema and perlèche by sugar-containing saliva

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[1979] Engelhardt, W Haben die beim Diabetiker gehäuft auftretenden Infectionen durch Staphylokken und Hefen ihre Ursache in dem erhöhten Haut- und Schweisszucker? München med Wchnschr 80 2037 2038, 1933

[1980] Ballhöfer A Hautkrankheiten und Diabetes mellitus Inaug Diss Berlin, 1935

Vascular Disease.—Vascular disease of slight degree is extremely frequent in elderly and middle aged diabetics. Abnormally low temperature, pallor or cyanosis of the feet have been observed in approximately one half of 124 patients.[97] The capillary fragility of diabetics as demonstrated by the tourniquet test is greater at each decade than in nondiabetic groups.[98] Gottron emphasizes the increased capillary reactivity in diabetes.

In many cases gangrene of the toe or foot can be traced to minor skin ailments like epidermophytosis, interdigital fissure, ingrown toe nail, infected corns and calluses and small injuries from self treatment.[99] All these conditions should receive particular attention. Many of them are caused by improper and



Fig. 85. Diabetic gangrene.

tight shoes. Systematic foot hygiene in diabetics has been advocated by many physicians having wide experience in the management of diabetes. The institution of special foot clinics in large centers has undoubtedly helped to decrease the number of serious complications.[99, 100]

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[97] Nabie, M.: Diabetes Mellitus as Observed in 100 Cases for 10 or More Years. Peripheral Vascular Findings in 60 of These Cases, Am. J. M. Sc. 209: 23-25, 1945.

[98] Beaser, S. B., Rudy, A., and Seligman, A. M.: Capillary Fragility in Relation to Diabetes, Hypertension and Age, Arch. Int. Med. 73: 18-22, 1944.

[99] Joslin, E. P.: Treatment of Diabetes, Philadelphia, 1937, Lea & Febiger.

[100] Brandaleone, H., Standard, S., and Ralli, E. P.: Prophylactic Foot Treatment, Ann. Surg. 106: 120-124, 1937.

In these foot clinics the patients are educated to follow a daily morning routine of a warm foot bath without or with little soap followed by an alcohol rub and dusting with boric acid foot powder They are advised to massage their feet with lanolin at night. Epsom salt should not be used for the foot baths because it makes the skin dry Commercial corn remedies should not be applied and blisters not opened The toenails should be clipped properly Foot exercises consisting of a series of movements of the toes feet and legs are considered im portant if any vascular disease is present All exercises are done six times and if there is a tendency to coldness the exercises should be done twice a day An important part of the exercise is the alternating raising and hanging down of both legs for three minutes. Contrast baths of the feet are recommended The patient should begin with 105° F (40 5°C) and change five times to 50° (10°C) keeping the feet one minute in each bath and finishing with the warm bath He should keep his feet warm with stockings and not with hot water bot tles. Expert care should be taken of abnormal toenails calluses corns and my cotic infections. Extremely well fitting shoes and comfortable stockings are important. No walking barefoot no circular garters or bandages and no metal arch supporters are permitted

Impending gangrene will usually be diagnosed by observing the following signs [illegible]

1 The pulsation of the peripheral arteries especially of the dorsalis pedis Both sides must be compared Good pulsation does not preclude gangrene of a toe because a more peripheral part of the artery may be occluded. Absence of pulsation does not always mean impending gangrene because a collateral cir culation may develop

2 If the color of the elevated and dependent extremity remains the same the prognosis is relatively good whether the pulse is palpable or not. Pallor on elevation slow recoloring on return to horizontal position and purplish dis coloration of the dependent extremities means extensive circulatory disturbance. The level of the abnormal discoloration indicates the approximate level of oc clusion

3 The skin temperature is taken with special thermometers or by running the hand (ulnar side) from the thigh to the toes One should always compare both sides A gradual fall of the temperature is normal but a sudden change is of the same significance as a level of discoloration

4. The histamine test consists in scratching through a drop of histamine solution on both sides and on various levels or in ntradermal injections. The wheal and flare formation is supposed to be in inverse proportion to the degree of circulatory impairment

Diabetic gangrene does not occur in the lower extremities only and it is not entirely a disease of old age. Gangrene of many other parts of the body surface are on record. On the face gangrene may at first resemble erysipelas and later turn into a deep slough frequently with a fatal outcome particularly

[illegible] Grodinsky M Infection and Gangrene of Extremities Diagnosis and Treatment Am J Surg [illegible] 1939

PLATE IX

1 I Enlarged pigmentation of the hand atroph and senile purpur Ecchymoses appe on slight trauma, g percussion with rubber tipped hammer

Necrobiosis lipoidica diabeticorum (Urbach-Oppenheim) (Courtesy Dr L. Babalian)

3 Diabetes Infected toenail and early stages of g grene

4 Diabetes three da later g grene seems localized

5 Female ged 21 ar Xanthoma diabeticorum, small large lesion. Blood cholesterol 810 mg per cent

6 Female ged 21 y ars Xanthoma diabeticorum









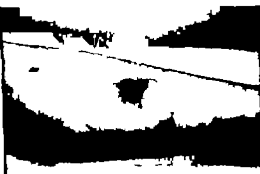




PLATE IV

if the cheek is involved.[1966] Loss of lips ears and particularly of the nose, as well as perforation of the septum and of the palate have often been reported Gangrene of the penis of the vulva and[1967] of small and large superficial or deep areas of the skin are known The superficial gangrene which occurs in small patches is called ecthyma. Though rarely diabetic gangrene may occur very early in life. Trauma plays a role in unusual sites of diabetic gangrene

The *treatment* of diabetic gangrene is mainly a surgical problem After drying of superficial necroses with subgallate of bismuth or other means the sores should be dressed with ointments containing as much cod liver oil as possible

In every case of beginning or impending gangrene pancreatic extract (Pancreatic hormone Grant or Sharp and Dohme's pancreatic tissue extract) should be given a trial. One to 3 c.c. are given daily or on alternate days. Padutin another pancreatic enzyme-free preparation is given by injection and by mouth. Wolffe[1968] recently reported 100 cases of gangrene that had received treatment with enzyme-free pancreatic extract. Eighty-eight per cent of the beginning dry gangrene and sixty three per cent of the more severe cases with not more than two toes involved were healed. The majority of these cases were diabetics. The pancreas contains a vasodilatory substance which is able to neutralize the rise in blood pressure produced by epinephrine It furthermore aids in fat metabolism by lowering the blood cholesterol and blood phosphatides. This substance is not identical with choline nor histamine. It may be identical or partly identical with the alcoholic, fat and insulin free neutral pancreatic extract, Lipocaic,[1969] which lowers lipemia and allows depancreatized insulin treated dogs to survive for longer than two to three months without the feeding of fresh pancreas.

Diabetic Ulcer.—Trophic ulcer of the foot is not infrequently found associated with diabetes The diabetic ulcer is not different in its appearance from other trophic foot ulcerations. It develops most often on the dorsum or the plantar surface of the big toe or at points of increased pressure The patients are often overweight rarely young Besides the care of the obesity exercises to improve the circulation and the topical application of cod liver oil are indicated Well-fitting shoes and protection from cold are most important.

Pruritus.—Pruritus is, especially in women[1970] such a common diabetic dermadrome that the urine should routinely be tested for sugar in all cases. In all stubborn and unexplained cases blood sugar tests should be done. More than fifty per cent of the cases of pruritus sine materia" show patho-glycemic curves.[1971] Besides the dietary and insulin treatment French authors have

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[1966] Millett, J Diabetic Gangrene of Face. 2 Fatal Cases, J.A.M.A. 113 1143, 1939

[1967] Ellis, O W W Occurrence of Diabetic Gangrene in an Unusual Location, J.A.M.A. 103 2183, 1934

[1968] Wolffe, J B Pancreatic Extract in Treatment of Gangrene, Am J Surg. 43 109-116, 1939

[1969] Dragstedt, L R Van Prohaska, J and Harms, H. P Substance in Pancreas (Fat Metabolizing Hormone) Which Permits Survival and Prevents Liver Changes in Depancreatized Dogs, Am J Physiol 117 175-181 1936

[1971] Campbell, G Gordon Relation of Sugar Intolerance to Diseases of the Skin, Brit. J Dermat. 43: 297-304 1931



Fig 255 Ulcus diabeticum



Fig 256



Fig 257

Fig 256 Ulcus diabeticum

Fig 257 Same ... after ... weeks of diet and insulin treatment



Fig. 158. — Felon in uncontrolled diabetes



Fig. 159. — Pyoderma in uncontrolled diabetes

reported successful x ray therapy to the splanchnic areas.[illegible] Spleen extract too has been advocated. *Pruritus has been observed not only in hyperglycemia but also in hypoglycemia.*[illegible] Cuklberg and Hannisdal treated such cases successfully *with glucose injections and insulin.*

Furuncles and Carbuncles have always been considered common in diabetes. This has been statistically confirmed by Greenwood,[illegible] who found the incidence among 500 diabetics about twice as high as the general average of the hospital patients (2 per cent compared with 1.2 per cent), and 7 times higher when furuncles and carbuncles in the history were counted. Williams,[illegible] who tried to prove that pyogenic infections are no more common in diabetics than in normals, showed that boils and carbuncles occur in 2.3 per cent of hospitalized diabetics. This figure is about four times the percentage of the general hospital average.

Tauber,[illegible] who compared the incidence of furuncles and carbuncles in about 500 hospitalized cases of diabetes with the incidence in 500 patients with normal or rather low blood sugar levels, found it to be twice as high among the latter. He also found a diet rich in carbohydrates (Wenckebach's diet), liver extract and daily intravenous injections of 500 c.c. of 5 per cent dextrose solution very helpful. Tauber's[illegible] figures have so far not been able to destroy the general and deeply rooted opinion that furunculosis is a frequent feature of uncontrolled diabetes.

Stomatitis.—Rudy and Cohen[illegible] examined the mouths of 403 diabetics, 138 of whom were edentulous. In uncontrolled diabetes, particularly if oral hygiene is lacking, heavy supra- and sub-gingival tartar deposits are often formed. *Gingivitis, swollen and bleeding gingival papillae and abscesses are common.* The teeth, which are often decayed, become loose but should be saved. The dental condition improves if the diabetes is controlled. No surgical procedure should be done before control of the diabetes.

The tongue in uncontrolled diabetes is often dry and coated. The saliva has been found acid because of the high content of lactic acid. Thrush on the palate and pharyngitis sicca occur.

Pruritus of the Meatus Acusticus is sometimes very annoying and may cause recurrent furunculosis of the external ear.[illegible]

[illegible] Goubs, F., and Bienvenue, A.: Traitement des prurits diabétiques et des diabétides par la radiothérapie sympathique. Bull. Soc. franç. de dermat. et syph. 38: 326-329, 1931.

[illegible] Dejaruna, J.: Pruritus und Pruriginöse Affektionen in ihren Beziehungen zum Kohlehydratstoffwechsel. Acta dermat. 21: 61-63, 1931. Zbl. 41: 76.

[illegible] Williams, J. R.: Does Diabetes Mellitus Predispose the Patient to the Pyogenic Skin Infections? J.A.M.A. 118: 1357, 1912.

[illegible] Rudy, A., and Cohen, M. M.: Diabetes Mellitus, Oral Aspects, New England J. Med. 219: 503-509, 1938.

[illegible] Majer, E. H.: Diabetes und Hals- Nasen- Ohrenkrankheiten, Wien. klin. Wchnschr. 50: 1841-1842, 1937.

[illegible] Kecht, B., and Ortbald, H.: Relation of Diabetes to Suppurative Conditions in Ear and Nose, Wien. klin. Wchnschr. 40: 1241-1243, 1936.

Miscellaneous —*Dupuytren's Contracture* of the palmar aponeurosis and Peyronie's disease (induratio penis plastica) either alone or together are rare but have a definite relationship to diabetes. Greenwood mentions the former having a percentage of 1.6 among his 500 diabetics. About twenty per cent of the patients with Peyronie's disease (induratio penis plastica) which often accompanies Dupuytren's contracture are diabetics. Nutritional deficiencies are reported to be more common in diabetes.[1997]



Fig. 200 —Atrophy of subcutaneous fat caused by insulin injection. (From Urbach, E. Skin Diseases, Nutrition and Metabolism, Grune & Stratton, Inc.)

Fat Atrophy —A peculiar sequel of diabetes is the fat atrophy at the sites of injections of insulin,[1998,1999] which occurs in about 7 per cent of the cases.[2000] It is a harmless but sometimes disfiguring condition consisting of the localized loss of subcutaneous fat. There is a decided feeling of looseness or emptiness in the subcutaneous tissues. Several such pits the size of a silver dollar may coalesce. Young diabetics with increased basal metabolism are especially inclined to develop this unusual response to insulin. Shelly thinks that the insulin may cause a sudden release of glycogen from the muscle which helps to burn the fat.[2001-2003] Much rarer than fat atrophy is its opposite, lipoma formation following insulin injections.[2004,2005]

[1997] Rudy A Unusual Case of Deficiency Disease in Patient With Diabetes Mellitus, Endocrinology 27: 208, 1940

[1998] Boberka, C J Fat Atrophy From Injection of Insulin, J.A.M.A 87 1646, 1926

[1999] Depisch, F Lokale Lipodystrophie bei lange Zeit mit Insulin behandelten Fällen von Diabetes, Klin. Wchnschr 5 1965 1926

[2000] Alpert and Ferguson Local Fat Atrophy After Insulin, Endocrinology 24 741 1939

[2001] Shelly J A Insulin Atrophy (of Fat Tissue) Pennsylvania M J 40: 347-348, 1937

[2002] Wismett, E B. Diabetes, 366 Cases, J Iowa M Soc 20 99-103 1930

[2003] Frei, W Insulin Atrophy of Subcutaneous Fat, Arch Derma & Syph 37 824-828, 1938.

[2004] Rowe A H and Garrison, O. H. Lipodystrophy Atrophy and Tumefaction of Subcutaneous Tissue Due to Insulin Injections, J.A.M A. 99 16-18, 1932.

[2005] Oellerstedt, X Zirkumskripte Hyperplasie des subcutanen Fettgewebes als lokale Folge von Insulin-Injectionen Endokrinologie 10 412, 1932

The patient in hypoglycemic shock perspires freely or even excessively while the skin remains dry in diabetic coma.[11,1996]

Xanthoma Diabeticorum is a rare condition. Joslin[11] observed only six cases among 1,000 cases of severe diabetes. The patients are mostly younger males. The xanthomas appear quite suddenly, usually in large numbers on the extensor surfaces, the palms and the soles. The individual lesion is a small papule, the size of a pinhead to that of a grain of wheat, rarely larger, red in color with a yellow center which looks pustular but is xanthomatous. They often have in-



Fig. 361. Female aged 21 years. Xanthoma diabeticorum [illegible]

flammatory bases and itch moderately. The histology shows intra and extra cellular deposits of fat with more inflammation and fibrosis than in primary xanthomas. Thannhauser and Magendantz[1997] classify the diabetic xanthoma with the secondary lipidoses, which means they are a complication of a lipemia which can be caused by diabetes as well as by pregnancy, icterus, nephritis or other conditions. The diabetic xanthoma responds to diet and insulin (see also chapter on lipidoses).

Necrobiosis Lipoidica Diabeticorum (Oppenheim-Urbach).—It is remarkable that a conspicuous, characteristic and not extremely rare dermatosis remained undescribed until 1929 when Oppenheim[1998,1999] presented a case of a

[1996] Worth, J.: Common Acne and Insulin Hypoglycemia. J. A. M. A. 100: 971, 1933.

[1997] Thannhauser, S. J. and Magendantz, H.: Different Clinical Groups of Xanthomatous Diseases, 22 Cases. Ann. Int. Med. 11: 1662-1746, 1938.

[1998] Oppenheim, M.: Eine noch nicht beschriebene Hauterkrankung bei Diabetes mellitus (Dermatitis atrophicans lipoides diabetica). Wien. klin. Wchnschr. 43: 314-318, 1930.

[1999] Oppenheim, M.: Ueber eine bisher nicht beschriebene mit eigentümlicher lipoider Degeneration der Elastica und des Bindegewebes einhergehende chronische Dermatose bei Diabetes mellitus (Dermatitis atrophicans lipoides diabetica). Arch. f. Dermat. u. Syph. 166: 576-583, 1932.

degenerative skin disease in a diabetic. Urbach [illegible] in presenting another case three years later emphasized the presence of lipoid substances in necrobiotic foci. He related these findings with the disturbance of the fat metabolism in diabetes

The lesions start as small red papules which grow slowly into irregular plaques from one to several inches in diameter In their mature stage they are waxy or mottled with a red yellow center The border is violaceous with a red or brown areola. Subcutaneous nodules may be covered with normal skin The surface



Fig [illegible] —Necrobiosis lipoidica diabeticorum (Urbach-Oppenheim) From Urbach E Skin Diseases, Nutrition and Metabolism, Grune & Stratton, Inc)

of the older plaques is usually traversed by fine telangiectatic vessels The plaques are quite hard especially along the edges. They are not elevated but the center of the lesions is flat or depressed The surface of the older lesions is shiny as if covered with collodion There is hardly any scaling Ulceration of the center may occur There is a tendency to heal slowly with an atrophic scar but this may take many years.

The average number of lesions runs from a few to a dozen They are most often located on the lower legs Lesions on the hands and in other regions have been described but none on the face Itching or pain is never mentioned tenderness usually being the only complaint

[illegible] Urbach, E Lipoidstoffwechselerkrankungen der Haut Handb d H Ch. [illegible] 1932
[illegible] Urbach, E Necrobiosis diabetica Eine neue diabetische Stoffwechseldermatose Zbl [illegible] 1932
[illegible] Urbach, E Eine neue diabetische Stoffwechseldermatose Necrobiosis lipoidica diabeticorum, Arch. f Dermat Syph. [illegible] 1932

The histology of necrobiosis lipoidica diabeticorum is of great interest. The primary phenomenon seems to be an intense localized angiitis. There is an inflammatory thickening of the vascular wall which leads to gradual occlusion of the blood vessel, particularly of the small arteries, with slow necrosis of the areas involved. The collagenous fibers become waxy and swollen and the nuclei disappear or stain but poorly with eosin. The elastic fibers deteriorate. Hemosiderin is present, explaining the brownish hue of the older lesions. The necrobiotic areas become impregnated with fat droplets which lie mostly but not



Fig 262 Uncontrolled diabetes, obesity, hypertension, lichen [illegible] rash

always extracellularly, sometimes surrounding the vessels in a certain distance.[illegible] Lymph capillaries stuffed with fat have been demonstrated. The droplets stain bright orange red with Sudan III, while the necrotic collagen is dull brown. Foam cells as in xanthomas, calcium deposits and giant cells have been observed,[illegible] mainly in the periphery of older lesions.

[illegible] Oettgen, H. Dermatitis Atrophicans Lipoides Diabetica, Med. Klin. 35: 143, 190 1939

[illegible] Nicholas, L. Necrobiosis Lipoidica Diabeticorum With Xanthoma Cells (Case With Pulmonary Tuberculosis), Arch. Dermat. & Syph. 48: 606-611 1943

Both neutral fats[illegible] and doubly refractory cholesterol have been demonstrated. High blood lipids especially cholesterol, have frequently been found. The fat in the necrobiotic tissues is probably deposited from the blood.

Ninety of the approximately one hundred cases so far presented were diabetics. There is a preponderance of the female sex.

The usual antidiabetic treatment does not seem to influence the condition but a diet low in fat as advocated in certain xanthomas has been recommended.[illegible]

Diabetic carotenemia or *xanthosis* diabetica (see carotenemia) is probably the most common diabetic dermadrome. It has long been considered harmless, and explained by the fat and vegetable diet of the patients. Recently Rabinowitch[illegible] found among 1 014 diabetics fifty nine cases of xanthosis, thirteen of whom had never been on special diets prior to the detection of this skin condition. The percentage of carotenemia in diabetics is probably much higher when the diagnosis is based on increased serum carotin and not only on clinical discoloration. Being a frequent accompaniment of severe diabetes, cardiovascular disease, insulin edema, resistance to insulin and hypercholesterolemia it suggests an unfavorable prognosis for the diabetes. The disturbance of the lipid metabolism in diabetics, the failure to synthesize vitamin A from its precursor carotin and possibly disturbed excretion of the carotin seem responsible for the accumulation of the lipochrome in the body.

The Blood Sugar in Various Dermatoses

The blood sugar has been investigated in all common and many rare dermatoses. Except for the established diabetic dermadromes the results have been meager. In finding a high blood sugar level one should recall that inflammatory processes in the skin are able to raise the blood sugar.[illegible] The blood from capillaries of inflamed skin contains more sugar than from normal skin.[illegible]

In groups of eczema patients[illegible] a higher percentage of sugar intolerance has often been claimed but also denied.[illegible] Dermatitis intertriginosa, seems more than other types of eczema correlated to sugar intolerance.[illegible]

[illegible] Zeisler, E. P. and Caro, M. R. Necrobiosis Lipoidica Diabeticorum, Arch. Dermat. 30 796-812, 1934.

[illegible] Grem, P. and Machacek, G. F. Necrobiosis Lipoidica Diabetica, Arch. Dermat. & Syph. 32 491, 1935.

[illegible] Urbach, E. Cutane Lipoidosen. Dermat. Ztschr. 66: 371-380, 1933.

[illegible] Rabinowitch, I. M. Carotinaemia and Diabetes, Canad. M. A. J. 18: 527-530, 1928.

[illegible] Milbradt, W. Zur Blutzuckererhöhung der Dermatosen, Dermat. Wchnschr. 94: 465-470, 1932.

[illegible] Eiddam, A. and Gallo, A. Vergleichende Untersuchungen über den Zuckerspiegel in den Kapillaren pathologisch veränderter sowie normaler benachbarter Hautbezirke, Dermat. Wchnschr. 94: 1185-1191, 1932.

[illegible] Allison, J. R. Hyperglycemia in Skin Diseases, South M. J. 30: 738-742, 1937.

[illegible] Hermans, E. H. and Hogewind, H. S. Bloedsuiker und Huidkrankheiten, Nederl. tijdschr. v. Geneesk. 75: 2909-2920, 1931. Ref. 39: 376.

[illegible] Baldie-Davis, H., and Wills, L. Abnormalities of Blood-Sugar Content in Eczema, Brit. J. Dermat. 37: 364-370, 1925.

Dry skin and "*chapping*" of the hands in cold weather should call attention to the possibility of a latent diabetes.[illegible] Chronic and unexplained eczema of the hands should be reason to search for diabetes.

It is an old experience that sugar and chocolate tend to make *acne* worse and that a diet low in sugar and starches is favorable for this condition. This is in accordance with Rosenfeld's[illegible] findings that sugar in the diet stimulates the secretion of the sebaceous glands more than fat. Schwartz,[illegible] Highman and Malinkin found high blood sugar levels in fifteen out of about thirty acne cases and also a similar percentage in seborrhea. Recently Semon and Herrmann[illegible] reported good results in treating acne with small doses of insulin.[illegible] They refer mainly to cases with menstrual exacerbations, emphasizing that the blood sugar tolerance curve during menstruation is flattened, reaching the fasting value more than three hours after the sugar intake. Many authors[illegible] more or less deny the relationship of acne and hyperglycemia. Lately healing of acne during hypoglycemic shock therapy of psychoses has been reported.[illegible] A great deal of evidence has been furnished demonstrating hyperglycemia in *psoriasis*.[illegible] Tauber was unable to confirm these findings. However there seems to be a relationship between diabetes and psoriasis which expresses itself in the occasional coincidence of both conditions in individuals and families. Greenwood[illegible] found 2.4 per cent of *psoriasis* among his 500 diabetics. This was ten times the percentage of the control group.

[illegible]Rost, G. A.: Hyperglycemia and Skin Diseases, Brit. J. Dermat. & Syph. 44: 67, 1932.
[illegible]Rosenfeld, G.: [illegible] ed. Dia. Zbl. Ges. Med. [illegible] 40, 1906.
[illegible]Schwartz, H. J., Highman, W. J. and Malinkin, H. C.: Sugar Content of the Blood in Various Diseases of the Skin, J. Cutan. Dis. 34: 159-165, 1916.
[illegible]Kerdén, G.: Dermatology in Diabetes, Dermatologica 87: 49-63, 1943.
[illegible]Strickler, A. and Adams, P. D.: Blood Sugar Metabolism in Certain Dermatoses, Especially in Acne Vulgaris, Arch. Dermat. & Syph. 26: 1-10, 1932.

Chapter XXIX

METABOLIC DISORDERS

Lipidoses

Chemical Data.—The following lipids occur in the organism

1 *Sterols* This important group which includes cholesterol and its esters the bile acids the sex hormones and some other organic substances has a characteristic structure with four rings.[illegible] Cholesterol is absorbed and synthesized in the body It is excreted in the bile and partly reabsorbed the larger part being transformed into coprosterol and eliminated with the stools Cholesterol always accompanies neutral fat.

2. Nitrogen and phosphorus-containing *phosphatides* such as lecithine cephalin sphingomyelin and the cerebrosides.

3 The *neutral fats fatty acids* and *soaps* These form the bulk of the body fat.

Normal (average) values for *lipids in the blood serum*[illegible]

	mg% Plasma		mg% Of total lipids
Total cholesterol	180	(110-150 Windaus) (100-210 Peters and Van Dyke)	34
Cholesterol esters	125	(40-70)	70
Lecithin	225		43
Total fatty acids	345	(190-420) (Peters and Van Dyke)	66
Total lipids	525	(700-800 Schaaf[illegible]) (570-820 Peters and Van Dyke)	100

Three per cent of the net weight of normal skin is made up of lipids Five to fifteen per cent of the total lipids is cholesterol Lecithin varies from only a trace up to 30 per cent of the total lipids.

The lipids in the serum depend on the intake and absorption the migration the deposition and disintegration of fat in the system and on the disturbances of the lipid metabolism in the cell.[illegible]

Pathology and Pathogenesis.—Several disturbances of the fat metabolism are accompanied by tumor-like lesions in the skin and in other organs which are called *xanthomas* While there are vast differences in the clinical appearance and in the severeness of the systemic involvement the histologic picture of all xanthomas is characterized by the presence of certain characteristic cells which are imbedded in a stroma.

[illegible] Thannhauser S J Lipidoses, Oxford Medicine, Vol. IV VIIA, New York, 1940, Oxford University Press

[illegible] Montgomery H., and Osterberg, A. E Xanthomatosis, Arch. Dermat & Syph. 37: 373-402, 1938

These cells, called foam cells, are large, at least of epithelium size. They occur mostly in nests, but diffuse infiltration to the degree of almost complete substitution of the normal tissue is known. The foam cells are constituents of the reticulo-endothelial system (Aschoff and his school, see Thannhauser[illegible]). Peri-adventitial reticulum and phagocytic connective tissue cells may become foam cells by being stuffed with fat droplets. In their mature stage they look alike. The foam cells may form giant cells of various types but there are no mitoses. Pigment, probably of blood origin, is frequently present. Cholesterol esters stain brown with Sudan III and dark blue with Nile blue sulfate. In polarized light they show the cross figures of double refraction.

The conceptions of the pathogenesis of the xanthomas and especially of the origin of the lipids in the foam cells have often changed[illegible]. Pollitzer and Wile[illegible] observed that the xanthomatous changes started in the adventitia of the small blood vessels. They concluded that the lipid substances in the xanthoma cells stemmed from extravasated blood and that their presence stimulated the connective tissue of the skin to hyperplastic growth. L. Pick and F. Pinkus[illegible], however, refuted the idea of hyperplasia or tumor formation. They suggested that the cholesterin infiltration of the cells was caused by the hypercholesterolemia which is often associated with xanthoma formation. However, xanthoma cases without hypercholesterolemia and the frequent hypercholesterolemia in diabetes, icterus, renal disease and pregnancy without xanthoma formation made it probable that hypercholesterolemia was not the only source of the fat in the foam cells. Aschoff and his school (lit. see Thannhauser[illegible]) demonstrated that *only the cells of the reticulo-endothelial system could become xanthoma cells*. Another advance was the *chemical identification* of the lipids in the various forms of lipidoses with cholesterol dominating in the xanthomas[illegible]. L. Pick[illegible] interpreted xanthoma formation as a "storage disease." The fat droplets which were taken up and stored like vital dyes by the cells of the reticulo-endothelial system apparently could not be disintegrated in the intermediary metabolism.

The decomposition of the blood lipids in the light of colloid chemistry is the center of the xanthoma theory of Bloch, Schaaf and Werner[illegible] propounded later especially by Schaaf[illegible].

These authors emphasized the importance of the *ratio of the lipid constituents* in the blood and in the tissues (free and bound cholesterol, phosphatides, true fats and perhaps other compounds as well). A change of the ratio of the lipid fractions would disturb the equilibrium of the lipid emulsion of the serum and lead to a coarsening of the lipid particles in the emulsion to decomposition and

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[illegible] Pollitzer, S., and Wile, U.: Xanthoma Tuberosum Multiplex, J. Cutan. Dis. [illegible] 235-241, 1912.

[illegible] Pick, L., and Pinkus, F.: Ueber doppeltbrechende Substanz in [illegible], Monatschr. f. prakt. Dermat. [illegible] 1908.

[illegible] Pick, L.: Classification of Diseases of Lipoid Metabolism and Gaucher's Disease, Am. J. M. Sc. 185: 453-469, 1933.

[illegible] Bloch, B.: Metabolism, Endocrine Gland and Skin Diseases, Special Reference to Acne Vulgaris and Xanthoma, Brit. J. Dermat. 43: 61, 1931.

[illegible] Schaaf, F., and Werner, A. J.: Die Pathogenese der Xanthome. Die Beziehungen von Cholesterin-, Phosphatid- und Gesamtfettgehalt des [illegible] zur Entstehung der Xanthome, Arch. f. Dermat. 162: 217-239, 1930.

precipitation of individual constituents in the tissues and finally to xanthomatous lesions. It was suggested[illegible] that the regulation of the concentration of fat emulsifying agents is a particular liver function the disturbance of which causes an impairment of the colloidal dispersion of fats in the blood serum and an increased tendency to throw the fats out of the emulsion Local contributory factors may modify the distribution of the xanthomas which develop in reaction to the deposits of de-emulsified fats. After formation of xanthomas the metabolic disturbance may subside leaving the xanthomas. In such cases xanthomas without symptoms of disturbed fat metabolism may be encountered.

Schaaf's conception was based on Spranger's[illegible] *investigations of emulsions* A fat in water emulsion is stable only if the concentrations of emulsifying agents are present in a definite ratio to each other Only under these optimal conditions can the fat droplets remain in the finest possible state of dispersion. Every variation in this ratio increases the readiness with which the fat separates from the water Cholesterol cholesterol esters and the phosphatides play an important role in the emulsification of fat in water In Ringer's solution containing proteins in quantities corresponding to those in the blood serum optimal distribution of neutral fat in the presence of cholesterol and cholesterol esters takes place only if this mixture of emulsifying agents contains 60 per cent cholesterol esters. In normal blood serum 60 to 70 per cent of the total cholesterol is present in the form of cholesterol esters. This fact stands in striking agreement with the optimal concentration of these two emulsifying agents

The ratio may also be changed by local factors such as trauma and inflammation Schaaf's conception of xanthoma formation is further based on the experimental production of xanthomas in animals. Xanthoma formation in patients with a normal total fat content or a normal total-cholesterol content is explained by the assumption of an abnormal ratio between the emulsifying agents especially cholesterol and cholesterol esters phosphatids, neutral fats and fatty acids The absence of xanthomas in hyperlipemia or hypercholesterolemia can be explained by the stability of the colloidal system in spite of the total increase of lipids due to the correct ratio of the constituents.

Montgomery[illegible] recently reemphasized the old experience that cutaneous xanthomas are not uncommonly seen in association with *hepatic disease* especially obstructive jaundice. (See Xanthomas.)

Thannhauser and Magendantz[illegible] and Thannhauser[illegible] emphasized and proved again with a great array of evidence both chemical and clinical that the specific lipids which form the cellular deposits are only in some cases present in excessive amounts in the blood serum They claimed that there is no proof of a colloidal decomposition of the serum or of the cell fluids resulting in precipitation which was the prerequisite of the hypothesis

They concluded that in one group of lipidoses which they called primary lipidoses the cause must be an intracellular disturbance of the lipid metabolism The fat droplets in the cells are in their opinion not supplied by the

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[illegible] Spranger W Zur physikalischen Chemie der Körperfett Ein Beitrag zur Physiologie der Verfettung. Biochem. Ztschr [illegible] 164-178, 1929

[illegible] Montgomery H Xanthomatosis, J Invest Dermat 1 [illegible]-341 1939

blood stream but formed and retained within the cell in the presence or absence of hyperlipemia. This theory found important support in the observation that *tissue cultures of xanthomas* are able to develop doubly refractile substances.[illegible] The primary lipoidoses are often hereditary. Thannhauser and Magendantz[illegible] did not deny that hyperlipemia may cause xanthoma. Xanthomas in hyperlipemia, of which the diabetic xanthoma is the best known type, were grouped together as secondary or hyperlipemic xanthomatoses.

Xanthoma

The cutaneous xanthomas are either solitary, localized in a few areas, or scattered over the body surface. The solitary xanthoma is represented mainly by the eyelid xanthoma (xanthelasma) which is almost always flat (Xanthoma planum). Xanthomas in other regions are usually prominent, either papular or tuberous (Xanthoma tuberosum multiplex). The xanthomas which are scattered over the body are mainly discrete shotty papules (Xanthoma disseminatum) which sometimes form large tuberous plaques.

Xanthoma planum palpebrarum (often called **xanthelasma**) is the only common type of xanthoma. All the others are rare conditions. It forms a single or, more often, a small number of oblong, soft, flat, hardly prominent, light yellow plaques. They surround the inner canthus in an arc which extends to the upper and lower lid. Rare atypical lesions may be red, brown or white, hard or tuberous. The author saw a case of xanthoma palpebrarum with tuberous nodules the size of a hazelnut so that the vision became disturbed. The lid xanthomas appear mostly in the fifth and sixth decades.

The common and reputedly harmless but popularly and medically suspected xanthoma palpebrarum did not prove so insignificant as often believed. Montgomery[illegible] studied 38 cases. More than 20 per cent had serious *cardiovascular disease*: hypertension, coronary sclerosis or angina pectoris. There was a definite increase in one or more of the blood lipids[illegible] and a consistent increase in lecithin. Montgomery[illegible] concluded that xanthoma palpebrarum is an accompaniment of systemic disease and that the condition is simply a variation of one of the types of xanthoma. Polano[illegible] found high or otherwise abnormal blood lipids in 25 per cent of the eyelid xanthomas. Thannhauser and Magendantz[illegible] call "forme fruste" of essential xanthomatosis a condition in which slight xanthoma of the lids, dark pigmentation around the eyes and xanthosis of the skin due to carotenemia are the only (and inconstant) dermadromes. However, there is a *high blood cholesterol* and a *low basal metabolism*. *Diabetes* and signs of angina pectoris are not infrequent findings. The incidence of eyelid xanthomas in middle aged *lepers* (10 per cent) is more than ten times higher than normal. It can be explained by high blood cholesterol and leprous involvement of the liver, which is encountered in almost all necropsies.

[illegible]Biedermann, W. and Hoefer, K.: Züchtung von menschlichem Xanthomgewebe in vitro, Arch. f. exper. Zellforsch. 10: 93, 1930.

[illegible]Curtis, A. C. and Berger, J. P.: Effect of Feeding Lipotropic Substance to Patients With Xanthelasma, Arch. Dermat. & Syph. 52: 252-256, 1945.

[illegible]Polano, M. K.: Die Xanthelasmatosen der Haut, Arch. f. Dermat. u. Syph. 181: 139-172, 1940.



Fig. 264



Fig. 265.



Fig. 266



Fig. 267

Fig. 264.—Xanthoma tuberosum multiplex. Some disseminated papules. (Courtesy Division of Dermatology, Department of Medicine, University of Chicago.)
Figs. 265-267.—Xanthoma. (Courtesy Division of Dermatology, Department of Medicine, University of Chicago.)

Xanthoma Tuberosum Multiplex and Xanthoma Disseminatum.—A tendency to form lines, stripes or oblong arrangement is a peculiarity of both the xanthoma palpebrarum and the disseminated types.[illegible] *Multiple xanthomas in small numbers (xanthoma tuberosum)* are typically localized on the extensor surfaces of the elbows, the knees and the heels. These xanthomas, except those of the palm, are rarely as flat as those of the eyelid. Papular, tuberous or lobulated forms on flat bases or short peduncles occur. The individual xanthomas may be crowded in ridges or furrowed plaques which may cover an entire axilla.[illegible] The xanthomas in the neighborhood of joints and tendons may be very firm, originating in the tendons or tendon sheaths, and may become adherent to the bones. The variety of features and the transitional types show that a sharp anatomical distinction between localized and multiple and also between flat and tuberous xanthomas is not possible.



Fig. 24. Xanthoma tuberosum multiplex. (Courtesy Division of Dermatology, Department of Medicine, University of Chicago.)

Montgomery studied 26 cases of *xanthoma tuberosum*. High blood cholesterol, familial histories and early coronary (27 per cent) or other forms of severe vascular disease (46 per cent) were, *though not constant, surprisingly frequent features*. *The combination of xanthoma tuberosum of the extensor surfaces* with occlusive arterial disease is known since at least 1873 (Fugge after Thannhauser;[illegible] also Barker[illegible]).

[illegible] Wise, F., and Garb, J.: Xanthoma Diabeticorum With Unusual Form of Eruption, Arch. Dermat. & Syph. 46: 723-731, 1942.
[illegible] Barker, W.: Occlusive Arterial Disease of Lower Extremities Associated With Lipemia and Xanthoma Tuberosum, Ann. Int. Med. 12: 1091, 1939.

The rare *disseminate xanthoma* is characterized by an abundance of small papular shotty lesions and plaques. This type favors the flexor surfaces, but may involve the entire skin Involvement of the sclerae and of the upper air passages occurs.



Fig [illegible] —Xanthoma tuberosum multiplex (Courtesy Division of Dermatology Department of Medicine University of Chicago

Herrmann and Nathan[illegible] described very thoroughly (1926) two cases of xanthomatosis. In one case small xanthomas were disseminated over the whole body surface and the blood cholesterol was normal In the other case the

[illegible] Herrmann, F and Nathan F Zur Frage der Xanthomatosis Arch. f. Dermat. u. Syph. [illegible] 573-601 1926



Fig. 270.—Four siblings affected with tuberous xanthoma, one of the extensor type. Father who had high blood cholesterol married second cousin. Of nine children, five were xanthomatous. One of the other children suffered from cardiac disease and had, like another non-xanthomatous child, high blood cholesterol. (From Bloom, D., Kaufman, S. R., and Stevens, R. A.: Arch. Dermat. & Syph., 1942.)

xanthomas were tuberous and limited to the extensor surfaces of the knees and elbows, to the extensor tendons of the fingers and to both Achilles tendons. The blood cholesterol was high a brother of the patient had hypercholesterolemia without xanthomas The authors emphasized that the two cases represented *two clinically and pathogenetically different types of xanthomatosis*

More recently Polano[illegible] Thannhauser and Magendantz[illegible] Montgomery and Osterberg[illegible] and other writers investigated the features of the two types. Tuberous xanthomas of the extensor surfaces in moderate number appearing early in life involvement of the tendons and tendon sheaths cardiovascular and liver disease, high blood lipids and dominant heredity characterize one type. Disseminate abundant small nodular xanthomas with predilection for the flexor surfaces involvement of the brain and nerve tissue causing diabetes insipidus and invasion of the bones larynx lungs and lymph nodes feature the

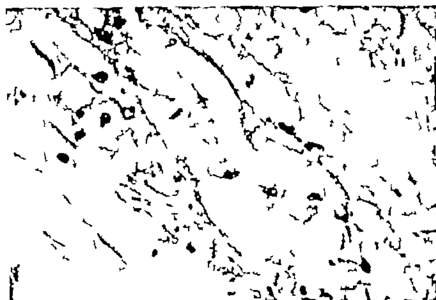


Fig. 271 — Hereditary xanthomatosis Foam cells in lipid deposit in the aorta. (From Bloom, D Kaufman, S R Stevens, R A Arch Dermat & Syph 1942.)

other type There is no jaundice These cases of the disseminate type usually have *normal* or high normal blood-cholesterol. The prognosis is particularly bad if the air passages are involved which may necessitate tracheotomy Thannhauser and Magendantz[illegible] emphasize that they were not able to find a single case described in which disseminate xanthoma was found combined with endocardial and vascular xanthoma. The situation is quite different in the extensor type. The xanthomatous involvement of the endocardium the valves and the large vessels particularly the aorta is the cause of the sudden deaths which occur very strikingly in the xanthoma families. The case of Arning is particularly well known The mother and five out of nine children had xanthomas. Three of

the children died at the ages of 16, 21 and 26 years of sudden heart attacks, two of them while dancing. Similar dramatic fatalities have been reported repeatedly.[illegible] The exhaustive necropsy findings in such a case have recently been published by Siegmund.[illegible] A girl of six years had been showing xanthomata tuberosa of the extensor surfaces of the buttocks and of the eyelids since the age of six months. Gradually the girl grew weaker and died from circulatory collapse. The heart valves, the root of the aorta and the coronary arteries showed lemon yellow xanthomas with cholesterol and calcium deposit. There was central congestion and atrophy of the liver but the Kupffer cells were free of fat. The kidneys showed xanthoma in the papilla. It is remarkable that the reticulo-endothelial system was free of fat. Two years later a brother 11 years old died suddenly. The post mortem findings were almost identical and so were those in one of the 5 tainted siblings in the case of Bloom, Kaufman and Stevens.[illegible]

Liver disease was found connected with xanthoma as early as 1850 by Addison and Gull.[illegible] Montgomery[illegible] demonstrated hepatic disease, particularly *obstructive jaundice, in 8 out of 55 xanthoma cases. Xanthomatosis in icterus* following neoarsphenamine treatment has been seen in several instances.[illegible] Biliary cirrhosis is apt to be seen with cutaneous xanthomas of the flexor surfaces. The cause of the obstructive jaundice is often found in xanthomatous changes of the bile ducts.[illegible]

Hyperlipemia is present in tuberous xanthoma but the normal ratio between cholesterol and cholesterol esters frequently remains undisturbed. Its inversion proves severe liver damage.[illegible] Phosphatides (lecithin) are likely to occur. In many cases of hepatic disease associated with cutaneous xanthoma in other location than in the eyelids, *palmar* lesions can be found. The eyelid xanthomas *in jaundiced patients often look lighter than the neighboring skin.*

Cutaneous xanthomas may undergo involution as the condition of the liver improves. Thannhauser and Magendantz[illegible] point out that frequently the cause of the liver disease in tuberous xanthoma is a *xanthomatous biliary cirrhosis.* Enlarged liver and spleen with jaundice of years duration, hypercholesteremia *with inverse ratio of cholesterol: cholesterol esters, together with xanthomata* tuberosa and plana of the extensor surfaces and buttocks are a characteristic diagnostic triad. If xanthomas of the tendon sheaths and tuberous xanthomas of the skin exist over a long time without jaundice, involvement of the liver is rare.

In cases of biliary cirrhosis caused by xanthomatous involvement of the liver an *eruptive universal papulopustular form of xanthoma* was seen, which in con-

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[illegible] Bloom, D., Kaufman, S. R. and Stevens, R. A.: Hereditary Xanthomatosis. Familial Incidence of Xanthoma Tuberosum With Hypercholesteremia and Cardiovascular Involvement. Sudden Death in Several Cases. Arch. Derm. & Syph. 45: 1-18, 1942.

[illegible] Siegmund, H.: Kardiovasculäre Xanthomatose als Todesursache bei Jugendlichen. München. med. Wchnschr. 85: 1617-1619, 1938.

[illegible] Addison and Gull: On a certain Affection of the Skin: Vitiligoidea (a) Plana, (b) Tuberosa. Guy's Hosp. Rep. 2nd Series, vol. 7, p. 265, 1851.

[illegible] Kolchar and Stokes: Multiple Xanthomas. Arch. Dermat. & Syph. 27: 133, 245, 1933.

[illegible] Nabl, O.: Formen der generalisierten Xanthomatose. Derm. Wchnschr. 94: 877-893, 1932.

trast to xanthoma without liver involvement was extremely itchy The soft small papules were scratched so that a prurigo-like picture resulted.

The multiple forms have been encountered early in life in many cases in childhood Urbach emphasizes that in childhood the fresh papular lesions are often bright red and not yellow due to the more abundant vascularization of the infantile skin The xanthomas rarely heal spontaneously

Hand-Schuller-Christian s Disease is a syndrome related to the xanthomatoses. It is characterized by the triad defects in the flat bones of the skull exophthalmus and diabetes insipidus.[illegible] Rowland[illegible] recognized the lesions of this disease as a special type of xanthomatosis with lipid storage in many parts of the reticulo-endothelial system. The infrequent involvement of the skin is surprising in this syndrome in view of the particular affinity for the skin in the other forms of xanthomatosis There are on record some cases with eczematous or purpuric, yellow or red-brown widespread papular rashes. A few developed xanthomata palpebrarum and disseminata. In one of the cases[illegible] the lenticular dermal xanthomas occurred in great profusion about the mouth and neck and the flexures of the big joints On the penis they were so numerous that a phimosis resulted Purpura may precede the xanthomas. In the eczematous lesions of one case foam cells were found[illegible] Gottron[illegible] interprets the Hand Schüller Christian dermatosis as a primary granulomatosis with secondary lipoid deposits in the later stages This closely follows the conception of Chester[illegible] who considered the granulomatous changes as the primary trouble and the lipid infiltration as secondary in the disorder Hypercholesterolemia has often been found

Secondary Xanthoma—(Xanthoma diabeticorum etc.) Thannhauser and Magendantz[illegible] emphasize that the eruptive form of xanthoma (xanthoma diabeticorum) is etiologically entirely different from all xanthomas due to primary xanthomatosis. It is a symptom of lipemia and may occur in diabetic lipemia as well as in lipemia associated with other diseases. It has been observed in cholesterolemia due to icterus pregnancy or nephritis. The difference between primary and secondary xanthoma is well illustrated by the rare cases of combination of both *In these cases the eruptive lesions disappeared under dietary treat*ment but the tuberous primary xanthomata remained

The eruptive sub-acute transitory and inflammatory character is the main distinguishing feature of the secondary xanthomas of which *xanthoma diabeticorum* is the best known (see diabetes)

Treatment of Lipidosis—According to Thannhauser and others the normocholesterolemic type does not respond to dietary treatment The cases

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[illegible]Christian, H. A Defects in Membranous Bones, Exophthalmos and Diabetes Insipidus Contributions Medical and Biological Research, vol. I New York, 1919 Paul B Hoeber Inc p. 390.

[illegible]Rowland, R S Christian Syndrome and Lipoid Cell Hyperplasias of the Reticulo-Endothelial System Ann Int Med 2 1377 1929 [illegible]

[illegible]Gottron H. Schüller-Christian Syndrome Arch. f Dermat. u. Syph [illegible] 1932.

[illegible]Wagner R Die Speicherkrankheiten (Thesaurismosen) Ergebn d. inn Med Kinderh [illegible] 1937

[illegible]Chester W Ueber Lipoidgranulomatose Virchow Arch f path. Anat. [illegible] 1930.

associated with hypercholesterolemia may respond to a diet low in cholesterol Such a diet is mainly vegetarian no animal fats being permitted

Lipocaic is a defatted alcoholic pancreatic extract studied by L. R. Dragstedt It seems to contain a hormone which influences high lipid values in the blood and it should be tried in hypercholesterolemic xanthomatosis

Diabetic xanthoma respond quite readily to diet and insulin The diet should avoid too much fat particularly animal fat

A trial should be given to the treatment of xanthomatosis with ultraviolet rays The effects seem to be of a general nature exceeding the radiated area [1964] X ray *treatment is locally effective in the tumors of Hand-Schüller-Christian's* disease rarely in other xanthoma The eyelid xanthomas may be treated locally

A few very rare diseases which are interpreted as lipidoses may be mentioned briefly



Fig 272 Lipoidosis cutis et mucosae (lipid proteinosis) Urbach-Wiethe) (Courtesy Dr Erich Urbach

Extracellular Cholesterinosis (Kerl Urbach)—This is a chronic disease coming on over many years. Maculopapular coalescent violaceous indistinct lesions and disseminated yellowish nodules are seen on the trunk. In addition there are tuberous tumor like hard scaly larger nodules on the extensor surfaces of the arms and hands. Some nodules appear on the soft palate

[1964] Rothmann, St Xanthoma diabeticorum behandelt mit Quarzlicht Zbl. 23: 26-27 1927

The fresh lesions are transparent papules with central vesicles. Spontaneous involution occurs frequently. The spleen is large and hard. Serum cholesterol may be abnormal.[2936] The lesions contained five times the cholesterol of the



Fig. 172.—Lipoidosis cutis et mucosae (Urbach-Wiethe). (From Ramos e Silva, J. Arch. Dermat. & Syph., 1943.)

normal skin. Histological examination revealed an enormous extracellular lipid infiltration (mainly with cholesterol) and destruction of the elastic fibers. Even the apparently normal skin showed lipid infiltration of the vascular walls. Montgomery[2937] after describing a similar case does not feel that the recognition of a new entity is justified. In contrast to Urbach's findings foam cells were present.

X-ray treatment was successful in a case of Frost and Anderson.[2938]

2938 Frost, K. and Anderson, O. R. Extracellular Cholesterosis of Urbach. Arch. Dermat. & Syph. 39: 1061, 1939.

Lipoidosis Cutis et Mucosae (Lipid Proteinosis) (Urbach-Wiethe).[1884] This condition has been shown to be a definite clinical and especially histological and histochemical entity.[1885-1887] About thirty cases have been published showing a surprisingly uniform syndrome. The disease affects the skin and the mucosa in all the reported cases with nodular or hyperkeratotic lesions. Hoarseness in the first years of life is a characteristic early sign. A somewhat varioliform eruption appears during infancy and leaves irregularly outlined soft depressed scars. The hair growth is sparse. Later there is brown pigmentation and a scattering of yellowish very small papules on the face, the nape of the neck and the dorsa of the hand. The papules are not follicular.[1888]



Fig. 274. Lipoidosis cutis et mucosae (Urbach-Wiethe). (From Ramos Silva, J.: Arch. Derm. & Syph., 1943.)

Irregular scarry ridges and patchy depressions give the face a characteristic "knitted" appearance at least in later years. Loss of the eyelashes, translucent nodules along the lid[1888] and indentations by scars add to the severe disfigurement. Especially in young persons some of the lesions bear crusts but there is no inflammatory border.[1888] The corners of the mouth show vertical grooves

[1884] Urbach, E. and Wiethe, C.: Lipoidosis cutis et mucosae, Virchows Arch. f. path. Anat., 273: 285-319, 1929.

[1885] Wise, F. and Rein, C. R.: Lipoidosis cutis et mucosae (Lipoid Proteinosis of Urbach), Arch. Dermat. & Syph., 37: 201, 1938.

[1886] Holzberger, M. B.: Case of Lipoidosis cutis et mucosae (Lipoid Proteinosis Urbach-Wiethe), Laryngoscope, 52: 290-293, 1942.

[1887] Ramos e Silva, J.: Lipoid Proteinosis (Urbach-Wiethe), Arch. Dermat. & Syph., 47: 301-326, 1943.

[1888] Campbell, A.: Lipoid proteinosis (Urbach-Wiethe), U. S. Nav. M. Bull., 42: 660-674, 1944.

There are elevated firm elastic brownish yellowish white or flesh-colored tumors on the extensor surfaces of the elbows and on the dorsal and lateral surfaces of the fingers. They are crowded together in warty mulberry like rough plaques



Fig. 278.—Lipoidosis cutis et mucosae (lipid proteinosis) (Urbach-Wiethe). Yellow nodular lesion beneath the tongue and infiltration of lower lip. (From Wile U J and Snow J S, Arch Dermat. & Syph 19 1)

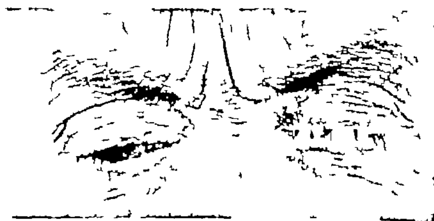


Fig. 279. Lipoidosis cutis et mucosae (lipid proteinosis) (Urbach-Wiethe). Numerous pearl white papules along the margins of the eyelids. (From Wile U J and Snow J S, Arch. Dermat. & Syph. 194

In some cases the papules undergo early involution persisting only on the elbow the knees and the hands. The lips show on their inner surfaces fairly firm, yellowish white plaques. Similar plaques and streaks occur on the palate in the pharynx and on the under surface of the tongue which is rigid and limited

in its motion by a deep seated infiltration and thickening of the frenulum The papillae are mostly lost.[illegible] Similar thickening symmetrically involve the tonsils and the larynx

In the majority of the cases either glycosuria or latent diabetes is present Heredity seems to play an important role Consanguinity of the parents and familial occurrences are on record Congenital hoarseness and developmental defects have also been observed

Laryngotomy because of severe dyspnea from scarring has become necessary in several cases

There can be no doubt that this is a characteristic syndrome The outstanding histological features in both the skin and in the mucosa are (Wise and Rein[illegible]) an infiltration with a lipoid substance surrounding the vascular walls with massive deposits and vacuolization of the infiltrating masses seen in paraffin section Foam cells and double refraction indicating cholesterol esters are absent The infiltration consists of a lipid probably bound to a protein

Bürger and Grütz[illegible] described a severe lipidosis with extremely high lipemia hepato-splenomegaly and a chronic *eruption* of small yellow elevated nodules on the extensor aspects and the buttocks The lesions mainly contained phosphatides but no foam cells and no doubly refractile lipids [illegible]

Gaucher's Disease is a slowly progressive often hereditary chronic lipidosis involving the spleen the liver and the bone marrow An uneven brownish tan pigmentation especially on the parts is usually noticeable Chloasma like often symmetric patches as well as streaky patterns have been seen [illegible] Such symmetrical pigmentations may form quite characteristic leaden-gray reticular gross patterns on the lower legs dotted with more intensely pigmented spots In advanced cases the skin of the pigmented areas of the legs is glossy and scaly sometimes ulcerated These pigmentations leave the soles heels and toes free but they involve the instep areas in a sharply outlined spat like fashion [illegible] There is a striking free margin just below the ankle Leg ulcers without varicose veins occur The mucous membranes may be pigmented but this is supposed to occur only if the adrenals are affected by the lipid deposits The pigment is melanin Brownish yellow triangular conjunctival thickenings occupying the interpalpebral space on both sides of the cornea but leaving a thin white stripe around the cornea appear slowly in the second decade These pingueculae together with bone changes and splenomegaly establish the diagnosis.[illegible] Purpuric tendencies occur at times [illegible] The specific lipid of Gaucher's disease which fills the large Gaucher cells in the involved organs is kerasin

Niemann Pick's Disease is another rare familial splenomegalic lipoidosis characterized by enormous accumulations of the diaminophosphatide sphingomyelin in the entire reticuloendothelial system The disease is fatal within the

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[illegible] Szodoray L Lipoid Proteinosis (Urbach-Wiethe) Dermatologica 83 373-386, 1941

[illegible] Bürger M and Grütz, O Ueber hepatosplenomegale Lipoidose mit xanthomatösen Veränderungen in Haut und Schleimhaut, Arch. f Dermat. u. Syph 166: 542-575, 1932.

[illegible] Bloem, T F Groen, J and Postma, C Gaucher' Disease, Quart J Med. 5 517-537 1936.

first two years of life The skin[illegible] of the infants is described as wrinkled pale and profusely sweating The subcutaneous fat disappears entirely The exposed parts and also the mucous membranes are diffusely pigmented and pigmented patches also occur in the mouth The pigment is melanin and possibly due to adrenal involvement.[illegible]

[illegible] Pick, L. Niemann-Pick's Disease and Other Forms of So-called Xanthomatosis, Am. J. M. Sc. 185 601-616, 1933.

Chapter XXX

METABOLIC DISORDERS

Hemochromatosis

Hemochromatosis,[illegible] *pigmentary cirrhosis in diabetes* and *bronzed diabetes* are terms mostly used to designate a disease characterized by the production of pigment in almost all organs, diabetes in 78 per cent of the cases and hepatic cirrhosis. The disease occurs almost exclusively (95 per cent[illegible]) in men, mostly in the decade from 45 to 55 years. The disease was encountered five times among 100,000 hospital admissions.[illegible] The onset is insidious with the symptoms of diabetes with abdominal pain or pigmentation of the skin.

The course depends on the diabetes and the cirrhosis. Before the advent of insulin about fifty per cent of the patients died in diabetic coma. Today the prognosis seems better since the outcome mainly depends on the course of the cirrhosis, *which may be protracted*.[illegible] *Primary cancer of the liver occurs in 7 per cent.*[illegible]

No specific treatment is known and though insulin may lengthen life the disease is ultimately fatal.

The striking pathological feature is the abundant production of pigment which is deposited in almost all organs though in varying amount. The most heavily affected organs are the liver, the pancreas, the adrenals, the salivary glands and the lymphatic nodes. There are two pigments present. *Hemosiderin* gives the iron reaction and *hemofuscin*[illegible] is an iron free melanin. The iron content of the organs which have been mentioned as the sites of the main deposit may be a hundred times higher than normal.

The etiology is not known. *Familial occurrence has been observed.*[illegible] Sheldon, who has reviewed 345 cases in a comprehensive monograph, classes hemochromatosis as an *inborn error of metabolism* concerning the cells which later in life begin the cirrhosis of the liver and of the pancreas.

Dermadromes. The skin participates in the general process of *pigmentation* though not nearly as much as the liver and the pancreas. Discoloration is absent in only one sixth of the cases. The melanoderma develops insidiously and is the initial complaint[illegible] in about one fourth of all instances.[illegible] It may precede the diabetic and hepatic symptoms by many years.[illegible] It is more

[illegible]von Recklinghausen, F.: Hemochromatose, Versammlung Deutscher Naturforscher Aerzt., Heidelberg 1889, Verh. d. ges. Naturforsch. p. 324, 1889.
[illegible]Sheldon, J. H.: Hemochromatosis, London, 1935, Oxford University Press.
[illegible]Cal, J. C.: Hemochromatosis, 6 Cases, Texas State J. Med. [illegible]: [illegible], 1940.
[illegible]Butt, H. R. and Wilder, W. M.: Hemochromatosis, A Report of Thirty Cases Diagnosed During Life, Proc. Staff Meet. Mayo Clin. [illegible]: [illegible], 1937.
[illegible]Lawrence, R. D.: Hemochromatosis and Heredity, Lancet 2: 1055, 1935.
[illegible]Becker, S. W.: Schamberg's Disease Associated With Hemochromatosis, Arch. Derm. & Syph. 24: [illegible], 1931.

often diffuse than patchy or freckled In many instances the pigmentation covers the entire body but it is more pronounced in the parts exposed to the light and in the axillae the nipples the umbilicus and the genital region As in Addison's disease scars may become heavily pigmented

The *color* varies considerably [3064] In about twenty per cent of the cases the color is described as bronze, ranging from a light bronzing to deep brown and even black. An equal group is characterized by the presence of a gray slate or bluish hue with a metallic reflection The face tends to acquire a metallic sheen more readily than the body which usually remains brownish The *metallic component* is more often seen in advanced cases The oral *mucosa* particularly of the cheeks, is often pigmented. The discoloration is more spotty than diffuse being brown or slate The lips and conjunctivae may also become pigmented

Except for the pigmentation the skin is not much changed Dryness, scaliness and pruritus may be troublesome [3071] *Purpura* occurs in about fifteen per cent.[3072]

Of great interest are the symptoms which indicate *endocrine* influences. They include atrophy of the testes and prostate impotence loss of axillary and pubic hair and thinning of the beard eyebrows and chest hair [3073]

The pigmentation of the nipples and of the genitalia must be interpreted in the same way Deficiency of urinary androgen and of adrenal cortical hormone has also been found These endocrine features seem to be accompaniments of the hepatic cirrhosis which is such an important part of the syndrome (see hepatic cirrhosis)

The pigmentation increases with the progress of the disease. Improvement has only rarely been reported most often in connection with insulin treatment.[3066]

As is the case in other organs the skin pigment is composed of hemosiderin and hemofuscin The hemosiderin appears microscopically in fine granules most densely accumulated in the membranae propriae of the sweat glands and in the vascular endothelium while the hemofuscin appears in coarse deposits in the epidermis and in the corium. The ratio of the two pigments varies.[3134] In some cases the hemofuscin is entirely absent (Roth after Kaufmann [30])

An *iron reaction in the living* skin has been devised by Fishback.[3077] Intradermal injection of a mixture of equal parts of 0.5 per cent potassium ferrocyanide and one-hundredth normal HCl produces a wheal which turns deep blue in the presence of iron after five minutes.

Diagnosis see Table I

Alkaptonuria and Ochronosis

A rare hereditary metabolic disorder in which the oxidation of the amino-acids tyrosin and phenylalanin is disturbed is called *alkaptonuria* The urine

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[3068] Walther Pigmentcirrhose (Bronzediabetes) Zbl. 80: 131.

[3071] Stetson, R F and Ferris, H. W Hemochromatosis and Purpura, Arch. Int. Med. 30: 223-226, 1922.

[3073] Labbé M Boulin, R and Ulery P Diabète bronzé avec atrophie des organes génitaux et chute des poils (syndrome hépato-pancréato-génital) Bull et mém. Soc méd. d hôp. de Paris 50 1574-1577 1934

[3077] Fishback, H R Clinical Demonstration of Iron in Skin, J Lab. & Clin Med. 25 98-99 1939

darkens on exposure to the air because of its content of homogentisic acid. This formation of pigment is closely related to the formation of melanin under normal and pathological condition After a long duration of alkaptonuria a dark iron free pigment melanin like in character[114] is deposited in the connective tissues predominantly in the tendons and cartilages. Virchow called this condition *ochronosis* The *ochronotic tissues cause characteristic surface dis-*



Fig 277 Ochronosis Lead colored spot in ear At right on transillumination Note dark cartilages (From Smith, J W J A M A)



Fig 278 Ochronosis Slate colored spots indicating the insertion of the tendons of the musculi recti

colorations wherever they are superficially enough situated This is the case in the sclerotics where slate-colored or even black scleral spots appear on both sides of the cornea but separated from the limbus corneae by a narrow white strip Thus *4 triangular figures* with dark centers result Obviously the site of these spots denotes the underlying insertion of the tendons of the rectus muscles. The influence of light may enhance the pigment formation

Slit lamp microscopy reveals deposits of pigment in the *cornea* [2975] Other though less frequent and conspicuous gray-greenish or even black discolorations are seen in the *ear* particularly the anthelix and concha, the tip of the nose and in the upper eyelids. Transillumination of the ears makes the cartilages visible as dark shadows.[2976] The ear ducts and the nasal septum may also be discolored The cerumen may be black [2977] and homogentisic acid has been found in it

Diffuse pigmentation of the face sometimes to the degree of bronzing bluish discoloration of the knuckles, the palmar eminences and the contact surfaces of the fingers have been observed [1138 2977 2978]

The *prognosis* depends on the development of destructive arthritis which occurs in the later stages.

Chronic *phenol poisoning* from prolonged wet dressings with 1 — 3 per cent carbolic acid may produce the same changes as spontaneous ochronosis.

The *morbid anatomy* in fully developed cases is dominated by the black discoloration of the entire cartilage system.

A low protein diet is advised in the management of ochronosis.[88]

Hyperuricemia—Gout

Purine substances are ingested mainly with liver and other viscera fish eggs and other foods rich in nucleoprotein A certain amount is synthesized in the body The end product of purine metabolism in the human organism is *uric acid* which is excreted in the urine mostly as urates.

Gout is an unexplained disorder of the purine metabolism The values of the normal as well as the gouty uric acid level in the blood vary remarkably Figures over 2.5 mg per cent [2979] over 4.5 — 6 mg per cent [1138 2980 2981] and over 8.5 — 9.5 mg per cent are samples of what is considered *hyperuricemia* by various authors. Deposits of urates in various tissues especially in and around joints [2982 2983] are a characteristic feature. Heredity seems to play a part.[2984] Ninety five per cent of the gout patients are *males* About 5 to 8 per cent of the patients with joint disease have gout [88 2985] It is still—as in Sydenham's time—[2986]

[2975] Smith, J W Ochronosis of Sclera and Cornea. Complicating Alkaptonuria Review of Literature and Report of 4 Cases, J.A.M A 120: 1282-1288, 1942

[2976] Swirsky M Y Ochronosis—Case With Alkaptonuria and Melanuria, Clinics 2: 1233-1252, 1944.

[2977] Poulson, V Ueber Ochronose bei Menschen und Tieren, Beitr z. path. Anat. u allg Path. 48 346, 1910.

[2978] Pick, L. Ochronose, Berl klin. Wchnschr pp 478, 509 556, 591 1906.

[2979] Kinsell, J and Haden, R. L Gout, Review of 62 Cases, M Clin North America 24 429-441, 1940.

[2980] Talbott, J H. Gout, New York, 1943 Oxford University Press.

[2981] McCracken, J H 30 Cases of Gout, Bull New England M Center 3 249-251 1941.

[2982] Hench, P S. Gout in U S A., Proc Staff Meet., Mayo Clin 12: 303-309 1937

[2983] Hench, P S Diagnosis and Treatment of Gout and Gouty Arthritis, J.A.M.A. 116 453, 1941

[2984] Bauer W and Klemperer F Medical Progress in Gout, New England J Med. 231 681-685, 1944

[2985] Hench, P S The Diagnosis of Gout and Gouty Arthritis, Proc. Staff Meet., Mayo Clin. 11 474-480, 1936.

[2986] Sydenham, Th The Works of Thomas Sydenham, vol. 2, London 1850, Sydenham Society pp. 123-163.

Fig. 279





Fig. 280

Fig. 279.—Gout, dormant ophus

Fig. 280.—Gout.

to some extent true that a higher social status (arthritis divicium of the old physicians) predisposes to gout [illegible] Though manual work and poverty do by no means protect against the trouble. Most writers agree that overindulgence in certain foods, as is common in the holiday season may precipitate an acute attack[illegible] in a gouty person

The clinical picture of gout is dominated by repeated acute and extremely painful attacks of arthritis mostly in the small joints. Involvement of one big toe (podagra) is a frequent event. In spite of the acute inflammation there is no suppuration and complete restoration to normal function is the rule The urinary excretion of urates is subnormal before and in the initial phase but increases rapidly during the attack.

In the chronic stage the attacks occur more frequently and last longer More and also bigger joints become affected and urate deposits deform and destroy the articular cartilages. *Tophi* as the demonstrable deposits of urates are called often appear in the neighborhood of joints, in and around tendons in the ears and occasionally in the subcutis.

Kidney function is often disturbed The prognosis depends on the amount of articular damage renal complications and the degree of cooperation by the patient in avoiding such foods which are prone to cause attacks. Colchicine relieves the acute attack, and cinchophen improves the output of uric acid in the interval although many consider it too toxic. Salicylates are widely used as a less dangerous substitute Hench[illegible] calls the therapy of gout, which has not advanced since the advent of cinchophen a reflection on medical progress

Dermadromes —The ruddy complexion and obesity[illegible] of the typical gouty man are often mentioned. Sydenham spoke of his thick shaggy eyebrows and his full crown of hair [illegible] The older literature emphasized and probably overrated the importance of gout in the etiology of dermatoses. Today to a large extent due to the skeptical attitude of J Jadassohn (1905) who called the evidence scanty and uncertain the only recognized skin manifestation of gout is the tophus of the skin. The tophi are rarely present before or during the first attacks, but they are almost invariably seen in chronic gouty arthritis.[illegible] Tophi in connection with the skin are seen in about one third of the cases about the small joints and on the ears. They are often found on the lateral aspects of the fingers, but also about the elbows, knees and heels. On the *ears* where they occur in the vast majority of the cases of tophaceous gout [illegible] they most frequently occupy the helix. The tophi are nontender very firm nodules of varying movability The size varies from a few millimeters to one centimeter in diameter but they are occasionally much larger The color of the skin over superficial tophi is pale yellow The nodules may ulcerate and in the contents microscopic needle-shaped crystals of sodium urate may be found.[illegible]

[illegible] McCracken, J P Owen, Ph S and Pratt, J H Gout, Still Forgotten Disease J.A.M.A. 131 367-372, 1946

[illegible] Brøchner Mortensen, K. 100 Gouty Patients. Acta med Scandinav 200 [illegible] 1941.

[illegible] Rutledge D J and Bedard, R E Criteria for the Diagnosis of Presumptive (Pretophaceous) Gout, Management of an Illustrative Case Proc Staff Meet Mayo Clin. 12: 149-154, 1937

[illegible] Lichtwitz, L. Gout, Bull New York Acad Med [illegible] 1934

[illegible] Christopher F and Monroe S. E Tophi of Heels J A M.A. 110 2149, 1938

The diagnostic value of typical tophi is great. Many clinicians have stressed looking at the ears in all cases of painful arthritis.

Pruritus is a frequent symptom of gout.[13] W. N. Goldsmith[illegible] calls gout the most frequent cause of itching, which certainly is not true in the U.S.A. Pruriginous eruption, urticaria and papular and bullous lesions have occasionally been seen paralleling the level of the hyperuricemia.[illegible] Sheaves of urate crystals were found in the lesions in some cases of papules and nodules of the skin of the lower legs.[illegible] The same is true of psoriasis,[illegible] erythromelalgia[illegible] and especially of eczema. Kromayer,[illegible] the last to report a large series of gouty eczema, saw its criteria in obstinacy, recurrence in the same spot, location in unusual places not subject to external irritation, multiplicity of patches and the coexistence of various arthritic and neuritic complaints. Unfortunately, his diagnosis and definition of gout are not up to the present standards, but one should not dismiss lightly his impressions nor those of other experienced clinicians. Garrod (after Bulkley[illegible]) found that 47 per cent of 2000 patients with gout had eczema. Bulkley[illegible] considered fully 30 per cent of his eczema patients as gouty.[illegible]

Despite these impressive figures the relationship of gout and eczema remains controversial. It is now generally considered of small importance.

The *blood uric acid in eczema*—and for that matter also in pruritus, psoriasis and urticaria—varies with a tendency to increased levels, especially in severe cases.[13] There is good reason to assume that in some of these cases the inflammatory and destructive processes in the skin are likely to be the cause of the hyperuricemia rather than its sequel.[illegible] Injections of uric acid into the blood of patients with eczema have been shown not to influence the skin lesions.[illegible]

Symmetric hyperkeratosis of the hands and soles, together with erythema of the palmar eminences, has been seen in several cases of hyperuricemia.[illegible] This condition occurs alone and also together with several internal disorders, e.g., hepatic disease, the menopause and pregnancy, so that no specific significance can be attached to the dermatosis. Many observations, mostly older than twenty years, are concerned with the role of hyperuricemia in psoriasis. Zorn[illegible] found that the scales in psoriasis contain a hundred times the amount of uric acid in the blood. He advises a purine free diet in eruptive psoriasis.

Tommasi and collaborators[illegible] have described an *alopecia* of the antero-lateral aspect of the *lower legs* about corresponding to the area supplied by the

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[illegible] Comel: Prurigo uratica. Gior. ital. di dermat. e sif. 79: 1083, 1939.

[illegible] Richter, W.: Harnsäure Diathese in Verbindung mit Hautkrankheiten. Dermat. Wchnschr. 101: 1867, 1935.

[illegible] Zorn, H.: Uric acid, Psoriasis and Gout. Dermat. Wchnschr. 96: 621-625, 1933.

[illegible] Markel, J.: Erythromelalgia Associated With Chronic Gout. Arch. Dermat. & Syph. 20: 72-74, 1979.

[illegible] Kromayer, E.: Ekzem und harnsaure Diathese. Deutsche med. Wchnschr. 61: 1037 1039, 1928.

[illegible] Rudolph, G. and Kolta, O.: [illegible] Untersuchungen bei Hautkrankheiten, Med. Klinik. 29: 1007 1012, 1931.

[illegible] Michael, J. C. and Nicholas, H. O.: The Behavior of Injected Uric Acid in Patients With Eczema, Arch. Dermat. & Syph. 19: 309-318, 1936.

[illegible] Barber, H. W.: Gout: Velar Involvement, Proc. Roy. Soc. Med. 31: 701, 1938, also 26: 407, 1933.

[illegible] Tommasi, L.: Alopecia of Peroneal Regions as Constitutional Sign of Neuro-arthritic Diathesis, Brit. J. Dermat. [illegible]: 1-9, 1910.

peroneal nerves together with slight atrophy of the skin and common baldness. These easily detectable hairless patches are supposedly suggestive of a high blood uric acid level.

Calcinosis of the Skin

It is difficult to characterize the internal disorder whose skin manifestations represent the various forms of cutaneous calcium deposits.



Fig. 231 —Calcinosis cutis (Courtesy Division of Dermatology Department of Medicine University of Chicago)

An exception is the metastatic calcinosis in which calcium deposits in the skin (striae) and other organs can be related to destructive bone disease e.g osteomyelitis[illegible] or myelogenous leukemia (Wels after Sutton and Sutton[illegible])

The term *chalk gout* (Minkowski after Steinitz[illegible]) is based on the similarity of nodular calcium deposits about small joints to the tophi of true gout. It is misleading in so far as an analogy to the uric acid metabolism in gout is not sufficiently apparent in the calcium metabolism in calcinosis.

[illegible] Jadassohn, J Ueber Kalkmetastasen in der Haut, Arch. f. Dermat. 100: 317 1910.
[illegible] Steinitz, H Calcinosis circumscripta und Calcinosis universalis, Ergebn. d. inn. Med. u. Kinderh. 35: 216-275, 1931

Cutaneous calcinosis occurs in two quite different types (Verse after Steinitz[illegible]) with relatively few transitional forms. In the so-called chalk gout or *calcinosis circumscripta* the calcium deposits appear as circumscribed nodules *mostly about the terminal phalanges of the fingers and on the extensor aspects* of the elbows. The volar surface of the finger tips is often the first location.[illegible] The legs are rarely affected except for the patellar area. The size of the nodules ranges from mustard seed to pea or even walnut size. Multiple deposits may simulate shots in the X-ray picture. The nodules are usually nontender. Acute painful inflammations of the para-articular tissues resembling gout may occur but they leave the joints and bones free.[illegible]

Superficial nodules may ulcerate and extrude calcareous material. The mouth of such sinuses is often surrounded by a hard yellow ring.[illegible] The nodules may become raised globular tumors[illegible] or the covering skin may be depressed and atrophic.



Fig. 2[illegible]. Localized calcinosis. Scarring and scar formation. (Courtesy Dr. O. Cooper.)

On the whole chalk gout in itself is not a severe disorder. The nodules may disappear spontaneously.[illegible] Life is rarely in danger. However 40 per cent of the cases[illegible] are combined with scleroderma, Raynaud's disease and acrodermatitis atrophicans.

[illegible] Epstein, E.: Idiopathic Calcinosis Cutis. Arch. Dermat. & Syph. 31: 347-377, 1936.
[illegible] Maloney, E. R. and Bloom, D.: Cutaneous Calcinosis, Arch. Dermat. & Syph. 23: 845, 1931.
[illegible] Swanson, W. W., Forster, W. O. and Iob, V.: Calcinosis Circumscripta, Am. J. Dis. Child. 45: 890-893, 1933.
[illegible] Weber, F. P.: Improvement in Cases of Calcinosis Universalis in Children, Brit. J. Dermat. 47: 400-404, 1935.
[illegible] Atkinson, F. R. B. and Weber, F. P.: Cutaneous and Subcutaneous Calcinosis, Brit. J. Dermat. 50: 267-310, 1938.

The female patients with chalk gout outnumber the males about 6 to 1 The disease occurs most often in persons beyond the thirty fifth year of life and the onset has repeatedly been seen connected with the menopause [illegible] It appears rarely in the young [illegible] at lactation or at puberty [illegible] Familial occurrence is known [illegible]

In the *diffuse* variety of calcinosis known as *calcinosis universalis* any part of the skin may become affected though there is a tendency to involve the neighborhood of the big joints. Symmetry is a feature and a decrease in the number of deposits towards the acra is often apparent



Fig. [illegible] —Male aged 83 years. Large subcutaneous calcareous plaques existing for many years. Secondary infection and sinus formation.

The lesions de elop in crops with fever and general reactions. The course is progressive so that finally almost the entire skin may become involved. Large calcareous plaques in or under the skin may form and ulcerate. Deeper structures may become affected and a septic syndrome with fever immobility of muscles multiple chalk abscesses and cachexia may result. The evacuation of large chalk abscesses may improve the picture. In some cases, several quarts of chalky matter could be drained from huge cold abscesses.[illegible] In chronic

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[illegible] Strandell Birger and Hesselman, B H Ein Fall von Kalkgicht, Hygiea 94: [illegible], 1932 [illegible] 43 467

[illegible] Pontoppidan, B Subcutane Kalkknoten bei pluriglandulärer Insuffizienz, Hospitalstid. [illegible] 12-13, 1931 [illegible] 1 413

[illegible] Oubrawer H. Beitrag zur Frage der Kalkansammlungen in der Haut, Dermat Wchnschr [illegible] 113- 6 1923

[illegible] Jacobowitz H Eine besondere Verlaufsform bei Calcinosis universalis, Ztschr f Kinderh. [illegible] 397-401 1932

[illegible] Gerhards F Ueber Kalkgicht Fall, Diss 1931 Marburg a. d. L.

[illegible] Weissenbach, R J Françon, F and Robert, P Calcifications [illegible] et arthrite [illegible] Paris méd 1933 II [illegible]

cases a combination of sinuses scars and ulcerations creates a picture which resembles scrofuloderma The prognosis is generally unfavorable[illegible] though *long remissions and occasional cures have been observed Combination with* scleroderma has been seen in 32 per cent of the cases of calcinosis universalis.[illegible] The disease is more frequently encountered in young persons and children[illegible] than in middle or advanced age [illegible]

Rosenberg [illegible] Brooks[illegible] and other writers who recently reviewed the subject feel that neither the theory of the deposition of calcium due to a disturbed calcium metabolism in analogy to uric acid in gout nor the theory based on the assumption of the deposition of calcium in already damaged tissues[illegible] have been convincingly proved The bony skeleton is usually intact and the blood chemistry has been found normal [illegible] Experimental hypercalcemia did not in the work of most of the experimenters lead to deposits [illegible] Except in scleroderma which accompanies only about 40 per cent of all the cases of calcinosis preexisting degeneration or necrosis has not been discovered In these cases the calcium metabolism is often disturbed

No specific treatment is known Abscesses should be drained since general improvement has occasionally followed A diet low in calcium seems sensible *None of the many procedures which have been tried on theoretical grounds*[illegible] has been confirmed or accepted.

Hypocalcinosis has been seen associated with impetigo herpetiformis and pustular psoriasis. (See chapter Parathyroids)

Amyloidosis

Amyloid is a protein which may occur in the skin[illegible] in a primary dermatosis (lichen amyloidosus) in the course of other especially senile dermatoses [illegible] or in certain tumors. Much rarer is cutaneous amyloidosis as part of the generalized amyloidosis which develops in chronic cachexias especially tuberculosis Cutaneous nodules[illegible] and erythemato—pigmentary or erythromelalgic changes[illegible] have occasionally been recorded but they seem to be very rare Also very rare

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Rémy Ren Sur un cas de granulations calcaires sous-cutanées, Bull et mém. Soc. de radiol. méd de France 20 437-440, 1932 Zbl 43 834

Hungerland, H Calcinosis universalis bei einem Kinde Zbl 54 203, 1936-1937

Rosenberg E F Chalk Gout J A M A 115 1791 1794 1940

Brooks W D W Calcinosis, Quart. J Med 3 293-319 1934

Thannhauser J Lehrbuch des Stoffwechsels und der Stoffwechselkrankheiten, München, 1929 J F Bergmann, p 603

Bielert Hagemann, E Die Calcinosen der Haut unter Berücksichtigung zweier Fälle von Acrocalcinose Diss 1932, Hamburg

Friedländer J [illegible] Untersuchungen des Gesamtmineralwechsels bei Calcinosis universalis, Deutsches Arch f klin Med 166 107 121 1930.

Gougerot and Carteaud Contribution à la pathogénie des granulomes calcaires Absence de réactions inflammatoires Résorption des sels calcaires injectés loin des lésions et dans les lésions, Bull. Soc franç de dermat et syph 39 701 704 1932

Sannicandro G La degenerazione amiloide della cute, Gior ital di dermat. [illegible] 74 1499-1534, 1933.

Freudenthal, W Amyloid in der Haut, Arch f Dermat. u. Syph 162 40-84, 1930.

Michelson, H. E and Lynch, F W Systematized Amyloidosis of the Skin and Muscles, Arch Dermat & Syph 29 805-830 1934

Flessinger N F [illegible]vet, J and Albaharry Cl Un cas d amylose hépatique et cutanée Bull. et mém. Soc méd d hôp de Paris 58 274-278, 1942.

is a peculiar form of *systemic amyloidosis* which not only produces an unusual dermatosis, but follows a different pattern in the distribution of the amyloid avoiding the spleen and the large glands which in the typical cases contain the largest deposits of amyloid Instead the smooth and the striated muscles



Fig. 284.



Fig. 285.

Fig 284 —Localized amyloidosis. (Courtesy Division of Dermatology Department of Medicine University of Chicago.)

Fig 285 —Amyloidosis cutis (lichen amyloidicus) (Courtesy Dr H. E. Kittredge)

including the heart are the site of widespread amyloidosis [illegible] Enlargement fissuring and nodularity of the *tongue* was present in all cases. There may be difficulty in closing the mouth and the *gait* may be shuffling The clinical aspect of the skin in some of the cases[illegible] is characterized by *transparent* or yellow waxy small high firm papules which cover some areas very densely

[illegible] Lubarsch, O Zur Kenntnis ungewöhnlicher Amyloidablagerungen, Virchows Arch. f path. Ana 273: 867-869, 1929

[illegible] Königstein, H Amyloid der Haut, Handb. d H. u. Gk, 4 3 284-357 1932

[illegible] O'Leary P A Montgomery H and Brunsting, L. A. Systemic (and Amyloidosis of the Skin, and Mucous Membranes Bence-Jones Proteinuria, Arch. Dermat. & Syph. 31 406-409 1935.

[illegible] Bosellini, P L. Sopra l'amiloidosi cutanea, Česká Dermat pp. 57-62, 1931 Zbl. 44 479.

[illegible] Mellow W Zur Klinik der systematisierten Amyloidose, Verhandl. d. deutsch. Gesellsch. f inn Med pp. 335-336, 1930.

The eyelid scalp the pubic and adjoining areas the palms the dorsa of the feet and other sites have been seen covered with the lesions which at first glance because of their tran parency give the impression of vesicles Atrophy telangi ectases and purpuric spots are other features In some cases the lesions were very firm large nodules[illegible] or large sclerodermatic plaques[illegible]

All the patients were middle-aged or older[illegible] Multiple myeloma and Bence Jones proteinuria have been found in some cases[illegible]

The presence of amyloid in the living skin can be demon trated by the subcutaneous injection of 0 1 per cent solution of congo red in saline The produced red spot fades within 4 days in normal skin but remains vi ible up to 12 days if amyloid is present at the site of injection[illegible]

The amyloid forms a band in the upper cutis the epidermis being atrophic and free of amyloid The vascular walls and the muscles contain large deposits The spleen and the large gland have no amyloid or only along the blood vessels.

Gottron, H Kreislaufstörungen und Hämorrhagien der Haut In Arzt and Zieler Die Haut und Geschlecht skrankheiten vol II Berlin, 1935, Urban & Sch[illegible] rzenberg pp [illegible]

[illegible] Gottron H [illegible] unter dem Erscheinungsbild einer Sklerodermie [illegible] Amyloidose der H[illegible] t Zbl [illegible] 1937 [illegible]

[illegible] M[illegible] A Amyloidose der Haut Zbl [illegible] 1936-1937

[illegible] Gottron, H [illegible] Haut Muskel-Amyloidose [illegible] dem Bilde eines Scleroderma amyloidosum Arch f Derma [illegible] Syph [illegible] 1932

Marchionini A and John, F Ueber [illegible] polikiloderm[illegible] Hautamyloidose [illegible] Diagnostik des Ha amyloids am Lebenden Arch f Dermat Syph [illegible] 1936

[illegible] Philips[illegible] nd Freeman A W Amyloidosis Cutis Lichenoides, Arch Derma & Syph [illegible] 1936

Chapter XXXI

METABOLIC DISORDERS

Vitamin Deficiencies

Avitaminosis A.—Vitamin A is a fat-soluble heat-resisting unsaturated alcohol which is easily destroyed by oxidation. It is formed in the liver from its precursors, the yellow or red carotenes which occur in widely differing amounts in fruits, vegetables and animal fats. The daily vitamin A requirement of the human organism is 3000-5000 I. U.

Deficiency of vitamin A causes night blindness because the visual purple and the visual violet develop from Vitamin A. Xerosis conjunctivae is another early ocular symptom occurring together with the cutaneous epithelial changes. A specific protective function of vitamin A against infections, which was assumed earlier,[illegible] is now doubted.[illegible]

The most often used test for vitamin A deficiency is the measuring of the dark adaptation of the eyes. This is done by determining the threshold amount of light which must be used to illuminate a given surface in order to render it visible. The readings after light and dark adaptation are then compared.[illegible] The value of the dark adaptation test for vitamin A deficiency has recently been questioned.[illegible] The determination of the concentration of vitamin A in the blood plasma will probably be a better indicator of deficiency than the dark adaptation,[illegible] but so far only little work with spectrophotometric determinations of the vitamin A content in connection with skin changes has been done.[illegible]

The fat droplets containing vitamin A are highly fluorescent in ultraviolet light, but lose this property rapidly in ultraviolet light.[illegible] Surprisingly enough

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[illegible] Scheer, F.: Ueber die Bedeutung der Vitamine in der Dermatologie, Zbl. 46: 657-681, 1933-1934.

[illegible] Ebert, M. H.: Vitamins in Dermatology, M. Clin. North America 26: 47-64, 1942.

[illegible] Pfannenstiel, W. and Scharlau, B.: Der Einfluss gesteigerter Vitaminzufuhr auf experimentelle Staphylokokkeninfektionen der Haut, Ztschr. f. d. ges. exper. Med. 71: 465-476, 1930; Zbl. 35: 622.

[illegible] Pfannenstiel, W.: Weitere Versuche über den Einfluss von Vitaminen und Calcium auf experimentelle Staphylokokkeninfektionen der H..., Ztschr. f. d. ges. exper. Med. 77: 818-826, 1931; Zbl. 39: 290.

[illegible] Sternberg, Th. and Pillsbury, D. M.: Influence of Avitaminosis A on Experimentally Produced Cutaneous Infections in Ra..., Arch. Dermat. & Syph. 36: 247-250, 1937.

[illegible] Brunsting, L. A. and Sheard, C.: Dark Adaptation in Pityriasis Rubra Pilaris, Arch. Dermat. & Syph. 43: 42-61, 1941.

[illegible] Carleton, A. and Steven, D.: Keratosis Follicularis, Arch. Dermat. & Syph. 48: 143-180, 1943.

[illegible] Walters, J. D.: Dark Adaptation in Skin Conditions, Ohio State M. J. 40: 834-836, 1944.

Rech, D. M., Brunsting, L. A. and Osterberg, A. E.: Use of Vitamin A Tolerance Test in Certain Cases of Dermatologic Disorders, Proc. Staff Meet., Mayo Clinic 21: 209-217, 1946.

[illegible] von Querner, F.: Der mikroskopische Nachweis von Vitamin im animalen Gewebe, Klin. Wchnschr. 14: 1213-1217, 1935.

in examinations with the fluorescence microscope vitamin A has been found to be absent from the epidermis even after the feeding of high doses.[n 1]

It is likely that vitamin A is concerned with the lipid. Experimental hyper vitaminosis A results in accumulation of cholesterol in the adrenals, the skin and other organs[n] so that lesions develop which are comparable to those of Schüller Christian's disease. Circumscribed alopecia is also a feature of this experimental disease.



Fig 298. Infant 16 months of age. Follicular hyperkeratosis in vitamin A deficiency with xerophthalmia. (From Frazier, C. N., Hu, C. K. and Chu, F. T.: Arch. Dermat. & Syph. 1943.)

Dermadromes.—Hyperkeratinization as an effect of vitamin A deficiency on the epithelium has been known for a long time (Mori after Schaaf[n]). In the rat it leads to the appearance of keratinized cells in the vaginal mucosa, a phenomenon resembling estrus.

In the human skin the effects of vitamin A deficiency are also dominated by hyperkeratinization.[n] Dryness caused by impaired function of the keratinized oil and sweat glands is the first symptom. Frazier and Hu[n] and Inde-

[n]Cornbleet, Th., and Popper, H.: Properties of Human Skin Revealed by Fluorescence Microscopy. The Normal Skin. The Vitamin A Content of the Skin, Arch. Dermat. & Syph. 46: 59-65, 1942.

[n]Collazo, J. A., and Rodriguez, J.: Hypervitaminose A durch Fütterung von reinem A Vitamin an junge Ratten, Klin. Wchnschr. 12: 1732-1734, 1933.

[n]Mashkilleison, L. N., Benyamovich, E. B., Krichevskaya, E. D., and Shamova, L. V.: Vitamins in Pathogenesis and Treatment of Skin Diseases, Am. Rev. Soviet Med. 3: 19-27, 1945.

[n]Frazier, C. N., and Hu, C. K.: Cutaneous Lesions Associated With Deficiency in Vitamin A in Man, Arch. Int. Med. 48: 507-514, 1931.

pendently Loewenthal[illegible] described a characteristic dermatosis which occurred frequently in persons who had lived on a diet deficient in vitamin A and who suffered from night blindness keratomalacia and/or xerophthalmia. The eruption which was called *phrynoderma* or toad skin by Nicholls [illegible] healed after treatment with vitamin A or an adequate diet.



Fig. 287 — Male aged 14 years. Diffuse follicular hyperkeratoses (phrynoderma) in vitamin A deficiency (From Frazier C N H C K and Chu, F T Arch. Dermat & Syph., 1943)

Phrynoderma consists of disseminated somewhat grouped *perifollicular papules* with a central keratotic plug or spine In severe cases[illegible] the papules are large flat or hemispherical sometimes acneiform without suppuration sometimes more like lichen planus. Slate colored hyperpigmentation may occur in and around the lesions. The eruption is usually abundant and symmetrical predominantly appearing first on the anterolateral aspect of the thighs and the

[illegible] Loewenthal, L J A A New Cutaneous Manifestation in the Syndrome of Vitamin A Deficiency Arch. Dermat & Syph 28 700-708, 1933

[illegible] Nicholls, L. Phrynoderma A Condition Due to Vitamin Deficiency Indian M. Gaz 68 681-[illegible], 1933

[illegible] Fasal, P Clinical Manifestations of Vitamin Deficiency in the Malay States, Arch. Dermat & Syph 50 160-166, 1944

posterolateral aspect of the upper part of the forearms spreading from here to the extensor surfaces of the arms and legs the shoulders abdomen chest back and buttocks.[714] Itching is a frequent complaint There i absence of visible sweating so that the articular folds become dry and scaly Diffuse branny scaling ashing " is also often noticeabl especially in Negroes [714] The colored skin is apt to lose its natural sheen [71] The lack of oiliness helps to differentiate this papular eruption from acne

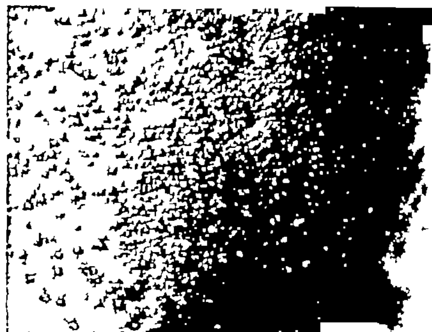


Fig. 255 Male aged 14 years Projecting spinelik follicular hyperkera oses I itamin A deficiency From Frazier C N H C K and Chu F T Arch Dermat & Syph 1943

Comedones are common not only in adolescents but also in older persons Brittleness and grooving of the nail [714, 714] is a feature of avitaminosis A. Loss of luster of the hair caused by dryness and alopecia are frequently observed phenomena [714, 71]

Phrynoderma usually precedes the *ophthalmic symptoms* [714] which sometimes are completely absent Pillat[71] describes a characteristic pigmentation of the

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[71] Lehman E and Rapaport, H O Cutaneous Manifesta ions of Vitamin A Deficiency in Children, J A M A 114 386-393, 1940

[714] Reiss, F Con ribution Cutaneous Manifestations of Vitamin A Deficiency Chinese M. J 50: 945-949 1936 Zbl 55 758

[714] Gill, Alopecia Circumscripta Due Vitamin A Deficiency Case Arch. Derma & Syph 51 110-111 1945

[71] Pilla A Ernährungslehre Edited by W Stepp Berlin, 1939, Julius Springer

[71] Frazier C N and Hu, C K Nature and Distribution According t Age of Cutaneous Manifestations of Vitamin A Deficiency (207 Cases) Arch Derma & Syph 33 825-852, 1936

[71] Pillat, A Ueber eine eigenartige Pigmentierung der Bindehaut bei den verschiedenen Formen der Vitami A—Mangelerkrankung der Erwachsenen, Graefe Arch 127 578-507 1931

conjunctivae most marked in the caruncula plica semilunaris, and the lower fornix. The pigmentation may outlast the deficiency state after treatment with vitamin A.



Fig. 290. — Follicular hyperkeratosis in vitamin A deficiency with xerophthalmia. (From Frazier, C. N., Hu, C. K., and Chu, F. T.: Arch. Dermat. & Syph. 1943.)

The *histopathologic* features are epithelial hyperplasia and hyperkeratinization with associated follicular keratinization and degeneration of the hairs as well as of the sweat and oil glands.[1133,1134] There is some inflammation in the corium but no pustulation. The disease is not rare among children[1134] as had been originally assumed. The closer the age groups are to puberty the more likely they are to be affected.[1134] This is in line with the well known tendency to follicular keratosis in acne juvenilis.

Among children with xerosis of the skin without phrynoderma the sexes are equally affected. In adult groups the patients are almost exclusively males.[1134] Straumfjord[1135] has tried to explain the formation of vernix caseosa by the absence of the antikeratinizing vitamin A in later fetal life. A small group of pregnant

[1133] Moult, F. H.: Histopathology of Rat Skin in Avitaminosis A. Arch. Dermat. & Syph. 47: 768-777, 1943.

[1134] Frazier, C. N., Hu, C. K., and Chu, F. T.: Variations in Cutaneous Manifestations of Vitamin A Deficiency From Infancy to Puberty. Arch. Dermat. & Syph. 48: 1, 1943.

[1135] Straumfjord, J. V.: Vernix Caseosa: A Manifestation of Vitamin A Deficiency. West. J. Surg. 48: -3, 1940.

women who were treated with high daily doses of vitamin A during the last six months of pregnancy had babies with less vernix than usual.

The response of phrynoderma and the other dermadromes to dietary *treatment* and vitamin A in daily doses of 100 000 to 300 000 I. U. is usually prompt within two to four months. The sebaceous secretion was often restored within two weeks. The recognition of a follicular keratosis as a specific manifestation of vitamin A deficiency by Frazier and Wu stimulated investigation of the nature of other follicular keratoses. Peck[illegible] found in eight out of ten cases of *Darier's disease* the blood vitamin A below normal and in nine cases he was able to improve the hyperkeratotic symptoms of this hereditary disease which up to then had been largely considered incurable. The vitamin A level in the blood rose under treatment with approximately 200 000 units daily.

Peck[illegible] believes Darier's disease to be a congenital disorder of the absorption of the vitamin A or of the conversion of carotene by the liver into the final product. Peck's work has been confirmed in several instances[illegible] of this rare dermatosis but resistant cases have also been found.[illegible]

The follicular keratosis in *pityriasis rubra pilaris* (Devergie's disease) prompted Brunsting[illegible] and Sheard to analogous investigations. In three cases the threshold levels of dark adaptation were much higher than normal. Under vitamin A treatment the night blindness and later also the cutaneous changes improved materially. The vitamin A content of the blood has several times been found low.[illegible] The good results of treatment with vitamin A have been confirmed in some cases.[illegible]

Treatment with vitamin A has been found beneficial in various forms of excessive or abnormal keratinization particularly in dermatoses which have the features of dryness (asteatosis) and follicular or other hyperkeratosis such as acne vulgaris, calluses, corns,[illegible] pruritus, kraurosis vulvae,[illegible] lichen pilaris,[illegible] keratotic lichenoid plaques of the legs, ichthyosiform erythroderma in Hodgkin's Disease with hepatic involvement,[illegible] scaliness of the external auditory canal,[illegible] nummular eczema,[illegible] brittleness of the nails,[illegible] dryness of the skin in diabetes[illegible] and keratosis blennorrhagica.[illegible] It has been recommended in ointments for the treatment of burns and slow healing wounds and ulcers.[illegible] The

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[illegible] Peck, S. M., Chargin, L. and Sobotka, H.: Keratosis Follicularis (Darier's Disease): Vitamin A Deficiency Disease, Arch. Dermat. & Syph. 43: 223-229, 1941.

[illegible] Peck, S.: Keratosis Follicularis (Darier's Disease) Treated With Vitamin A, Arch. Dermat. & Syph. 48: 433-438, 1943.

[illegible] Cornbleet, T., Popper, H. and Steigmann, F.: Blood Vitamin A and Cutaneous Diseases, Arch. Dermat. & Syph. 49: 103-106, 1944.

[illegible] Weiner, A. L. and Levin, A. A.: Pityriasis Rubra Pilaris of Familial Type, Arch. Dermat. & Syph. 48: 288-298, 1943.

[illegible] Straatsfjord, J. V.: Vitamin A: Effect on Acne, Northwest Med. 42: 219-223, 1943.

[illegible] Obermayer, M. E. and Frost, K.: Some Phases of Vitamin Therapy in Dermatology, Arch. Dermat. & Syph. 51: 309-312, 1945.

[illegible] Glassbrook, A. J. and Tomaszewski, W.: Ichthyosiform Atrophy of the Skin in Hodgkin's Disease: Vitamin A Metabolism, Arch. Dermat. & Syph. 50: 85-89, 194[illegible].

[illegible] Jones, J. H.: Vitamin Therapy, Laryngoscope 52: 805, 1942.

[illegible] Gross, P.: Nummular Eczema, Arch. Dermat. & Syph. 44: 1060-1077, 1941.

[illegible] Brazer, J. G. and Curtis, A. C.: Vitamin A Deficiency in Diabetes, Arch. Int. Med. 65: 90-106, 1940.

[illegible] Löhr, W.: Die Behandlung grosser flächenhafter Verbrennungen mit Lebertran, Chirurg 6: 963-970, 1934.

cod liver oil containing salves are an example Vitamin A in high doses has been found ineffective in ichthyosis[22]

All the mentioned *indications cannot yet be considered established*[2244] The therapeutic doses of vitamin A range from 50 000 to 200 000 units daily In spite of the fact that the blood serum level of vitamin A has been frequently



Fig 290 —Pityriasis rubra pilaris (Courtesy Dr M Jessner)

found to be low in widespread dermatitis eczema and psoriasis no curative effect of vitamin A therapy could be observed in such cases[2271] The level of vitamin A in the blood plasma of 55 patients with diverse dermatoses was essentially normal[2276]

[2244] Peck, L M Glick, A W and Chargin, L Vitamin A Studies in Cases of Ichthyosis, Arch Dermat & Syph 48 7-22, 1943

[2245] Marchionini, A and Patel, G Vitamin A— und Carotinhaushalt des menschlichen Blutserums bei Hautkrankheiten Arch f Derma Syph 175 19-427 1937

[2276] Cornbleet, Th Popper H and Steigmann, F Blood Vitamin A and Cutaneous Diseases Arch Dermat & Syph 49 103-109 914.

Carotenemia Xanthosis.—Carotinemia *aurantiasis* (Baeltz after Kaufmann[1078]) or *xanthosis* (Von Noorden and Salomon) after Salomon [1077] (manifests itself by a yellow discoloration of the serum and of large areas of the skin. The yellow color which may have canary, ochre or sulfur shades suggests at first glance icterus but the sclerae are white and the mucous membranes are usually of normal color with the exception of the palate. Another distinguishing feature is the distribution of the yellow pigmentation. The nasolabial fold, the axillae and the palms and soles are the sites of the most intensive discoloration, in slight cases the only sites. In contrast to icterus, pruritus is absent unless caused by diabetes. There are no complaints other than the disfigurement.

The urine is light compared with an icteric urine although carotene is excreted in the urine.

The history and physical examination almost regularly reveal that the patient had lived for a long time on a vegetarian diet, that he is a diabetic or both.

The yellow substance which causes the discoloration has long been identified as carotene. The carotenes are red, orange or yellow oxygen free hydrocarbons with 40 C-atoms, which by hydrolysis form the alcohol vitamin A. All green leaves (not the yellow leaves in fall) carrots, pumpkin, yellow squash, oranges, especially some Japanese varieties and many other fruits contain carotenes. Animals are unable to form carotene but they take it in and store it in the liver, the fat, the retina, the corpus luteum and the adrenal. It causes the yellow color of the butterfat, the body fat and of the egg yolk. Carotene does not appear in the sweat.[77] The horny layer of the epidermis has a marked affinity for carotene, which explains the normal yellow hue of the palms, soles and calluses.[1079]

Carotinemia has often been seen in babies fed with carrots. It was frequently observed during the First World War in Germany,[1077] where at times most of the population was compelled to live almost exclusively on rutabaga, carrots and other vegetables. It is also prevalent in the Japanese inland where the fish and meat supply is scanty. After feeding infants with carrots for a very long time the carotinemia may disappear in spite of continuing with the diet. The system apparently adjusts itself and becomes able to step up the splitting of carotene. The alimentary carotinemia, particularly in infants, is harmless and disappears quickly after a change in the diet (Diabetic carotinemia, see chapter on Diabetes).

Vitamin D (viosterol and activated 7-dehydrocholesterol) is stored mainly in the liver, but also in the skin and in other organs. One of the known functions of vitamine D is the maintenance of the absorption of calcium and phosphorus from the intestinal tract.[78] The most important vitamin D deficiency disease is rickets.

No dermatosis caused by vitamin D deficiency has been established. Therapeutic success with daily doses of 50 000 to 400 000 units have been reported in

[1077] Salomon, H.: Pseudoikterus nach Mohrrübengenuss, München. med. Wchnschr. 66: 364, 1919.
[1078] Kaufmann and Drigalski: Carotin-Vitamin A im menschlichen Organismus, Klin. Wchnschr. 12: 306-308, 1933.
[1079] Edwards, E. A. and Duntley, S. Q.: Pigments and Color of Living Human Skin, Am. J. Anat. 65: 1-33, 1939.

pemphigus[2159,2160] but confirmation has remained lacking[2161] The treatment has also been given a trial in psoriasis[2161,2162] and acne vulgaris. Though 80 per cent satisfactory results were claimed in a large series[2164] the method has not found general recognition[2165]

Vitamin E comprises a group of more than 130 substances.[1779] Experimental avitaminosis E manifests itself by sterility muscular dystrophy paralysis and other symptoms according to the animal used Many seed germ oils, particularly that of wheat contain vitamin E, which has so far not become of recognized dermatological importance. Its successful use in acrodynia has been reported[2166]

Vitamin K (menadione) occurs most abundantly in green leaves, e.g spinach alfalfa and cabbage It is also synthesized by several bacteria e.g Escherichia coli. Its absence inhibits the *prothrombin* formation in the liver When the prothrombin drops to about 10 per cent of normal in chicks kept on a vitamin K free diet the bleeding tendency appears[2157] In man obstructive jaundice through the absence of bile salts in the intestines impairs the absorption of adequate amounts of vitamin K and thus creates hypothrombinemia with a subsequent hemorrhagic tendency (Brown and Bancroft 1935 after Quick[2166]) Therefore the picture of avitaminosis K is that of hemorrhagi disease which may cause purpuric skin manifestations. In the adult it results most often from severe disease of the liver from short-circuiting operations or chronic diseases of the intestinal tract. For the role of vitamin K in the hemorrhagic disease of the newborn see chapter on newborn page 394

The Vitamin B Complex —According to Elvehjem[2168] the B complex consists of at least a dozen separate factors which vary widely in their chemical structure and physiological effects. Deficiency in any one of the B-vitamins is usually complicated by a deficiency in another B-vitamin or by a deficiency in som other vitamin[2169,2170]

Butterworth T Pemphigus Improvement Following Vitamin D Arch. Dermat & Syph. 41 630, 194

King, H and Hamilton, C M Pemphigus Controlled by Vitamin D Arch Dermat. & Syph. 39 1[illegible]-817 1939

Wright C S Vitamin D Therapy in Dermatology Arch Dermat & Syph. 43: 145-184 1940.

Lindsay H C Psoriasis Arthropathica Treated With Vitamin D Arch Dermat & Syph. 41: 921 1940

Maynard Vitamin Therapy i Dermatology Especially Vitamin D for Acne Arch. Dermat & Syph 41: [illegible]2-457 1940

Simpson, C Ellis, F A and Kirby Smith, H Vitamin D in the Treatment of Acne Arch. Dermat & Syph 41 435-437 1940

Forsyth G Pink Disease Treated With Wheat Germ, M J Australia 1: 78, 1942 Abst Arch. Dermat & Syph 46 773

Quick A J The Coagulation Defect in Sweet Clover Disease and in the Hemorrhagic Chick Disease of Dietary Origin A Consideration of the Source of Prothrombin, Am. J Physiol. 118: 260-271 1937

Elvehjem, C A Water Soluble Vitamins, Handbook of Nutrition Chicago 1943 American Medical Association

Jolliffe N Recent Advances in Clinical Applications of the B-Vitamins, J Am Dietet. A. 17: 8-11 [illegible]

Spies, T D Bean, W B and Ashe W F A Note on the Use of Vitamin B_6 in Human Nutrition, J A M A 112: 2414-2415, 1939

A *vitamin B deficiency should be suspected* in indigent groups in persons with peculiar food habits e g alcohol addicts, in persons who live mainly on sweets and in dietary faddists and in patients with diseases altering the vitamin B requirement Jolliffe[?] mentions in this connection prolonged abnormal strain manic depressive psychoses fever of long duration hyperthyroidism pregnancy lactation rapid growth diarrhea of long duration polyuria gastrointestinal fistulae and liver and stomach diseases

Thiamine —The richest sources of thiamine are yeast pork oatmeal peanuts and other seed and liver Spinach tomatoes oranges apples and white unfortified bread are poor in this vitamin Without the use of whole grain cereals or enriched bread it i difficult to meet the adult daily requirement of 1.5 to 2 3 mg [illegible] Symptom of thiamine deficiency [illegible] include anorexia fatigue insomnia nausea con tipation headache precordial distress and a group of more tangible neurological manifestations like symmetric polyneuritis especially of the legs followed by central symptom known as Wernicke s syndrome Finally there occurs a group of circulatory disturbances including edema serous effusions and circulatory collapse These circulatory manifestations occur in about one-third of the patient with polyneuropathy All the mentioned symptom together with their many variation form the *beriberi* complex



Fig 291 Cheilitis and perlèche in riboflavin deficiency Courtesy Dr O H Field J and The Upjohn Company

The only well established early and therefore important *skin manifestation in beriberi* is the burning of the soles of the feet and numbness of the dorsum and lower part of the ankle [illegible] Glossitis perlèche[illegible] and other skin manifestations probably belong to associated avitaminoses The expected pain relieving

[illegible] Sharples, L B Burning Feet in Labourers on Sugar Plantations in British Guiana, J Trop Med, 33: 356-360, 1930

[illegible] Strauss, M B Article in The Vitamins, Chicago, 1939 American Medical Association.

[illegible] Kagawa, S Ueber Rhagadenbildung am Mund [illegible] bei der B-A [illegible], Mitt d med. Gesellsch. zu Tokio 46 1158-1164 1932 Zbl 43 656



Fig. 291.—Loss of papillae filiformes and increased redness of the tongue in vitamin B deficiency (Courtesy Therapeutic Notes, Parke, Davis & Company.)



Fig. 292. Vitamin B deficiency. Loss of papillae filiformes resulting in slick fissured tongue. (Courtesy Wisconsin General Hospital.)

and curative effect of thiamin in herpes zoster and postherpetic neuralgia has failed to materialize.[194]

Riboflavin.—This vitamin is a yellow crystalline heat stable but light labile[71] substance. It function a an enzyme in ti u respiration. Liver milk and vegetables are the best sources. The daily minimal requirement can be met with one serving of liver or one quart of milk. Experimental ariboflavinosis causes retarded growth dermatitis and cataract in rats paralysis from myelin degeneration in chicks and dogs and opacities in the cornea of various animals.

Dermadromes.—In man vascularizing keratiti I usually the first to appear. It may be followed by glos itis and derma Iromes. Sebrell and Butler[195] gave eighteen adult women the so-called Goldberger Tanner diet[196] which does not contain meat milk or yea t but con ist mainly cf lard cornmeal casein



Fig. 291. Vitamin B deficiency. Perl he. Tongue: inflamed, fissured; papillae filiformes have started to disappear. (Courtesy Dr. Garn Cooper.)

tomato juice cod liver oil and other item low in riboflavin and nicotinic acid. Within three to four months ten out of the eighteen person developed pallor of the lips at the angles of the mouth without involvement of the buccal mucosa. This pallor was soon followed by maceration bilateral superficial transverse fissures extending downward from the angle in some in tances as much a one half of an inch. Thus typical perleche d veloped. There was l ttle inflammatory reaction. The lesion remained moi t and became covered with a yellow crust. The lips became eroded and red along the line of closure. Sebrell and Butler[195] called this labial affection *cheilosis*. In addition to the cheilosis there was a fine seborrheic desquamation on a light erythema in the nasolabial folds on the alae nasi in the vestibul of the nose and on the ears.

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[194] Rattner, H. and Rell, H.: Herpes Zoster and Vitamin B, J. A. M. A. 113: 2585-2586, 1939.

[195] Sebrell, W. H. and Butler, R. E.: Riboflavin Deficiency in Man, Pub. Health Rep. 53: 2282-2284, 1938.

[196] Goldberger, J. and Tanner, W. F.: Pellagra—Preventive Action of Dried Beans, Casein, Dried Milk and Brewer's Yeast, Pub. Health Rep. 40: 54-80, 1925.

Other authors[*] observed *filiform excrescences of a seborrheic nature* in the nasolabial folds and their surroundings resembling urea frost in conditions which they felt to be due to riboflavin deficiency.

The experimental cheilosis healed promptly on crystalline synthetic riboflavin, while nicotinic acid failed to cure it. Spontaneous cases of cheilosis are not infrequently found among alcoholics and other persons liable to become vitamin B deficient. Jolliffe et al. demonstrated that many of these spontaneous cases of cheilosis responded to synthetic riboflavin but not to thiamin, nicotinic acid or pyridoxin (also see Finnerud).

In some cases of ariboflavinosis the tongue has been found purplish red, fissured and with enlarged papillae. Riboflavin in doses of 2.5 to 50 mg given by mouth heals cheilosis from riboflavin deficiency, sometimes strikingly in a few days, but of course fails to do so when the perlèche or cheilitis are due to other causes, e.g., ill fitting dentures or sensitivity to light. Cheilosis is also a common feature of pellagra in children.

Sydenstricker and others have described *ocular* symptoms, especially an early vascularizing keratitis accompanied by inflammation of the limbic plexus and conjunctiva bulbi in the interpalpebral space. Photophobia is a characteristic complaint. The slit lamp is necessary for early diagnosis. The keratitis resembles the form often associated with rosacea, but it is bilateral, responds to riboflavin and shows a different vascular pattern.

The validity of the syndrome cheilosis, keratitis and glossitis as a manifestation of ariboflavinosis has recently been doubted because of the failure of riboflavin to cure it in 20 cases. Riboflavin has lately been recommended in the treatment of eczema.

Rats with chronic hyporiboflavinosis showed, in contrast to other avitaminoses, a heavy infestation with lice which disappeared after feeding them riboflavin.

Nicotinic Acid (Niacin). Pellagra.—Nicotinic acid (niacin) and nicotinic acid amide (niacin amide) are the components of two pairs of heat stable (Chick and Roscoe) coenzymes concerned with respiration and carbohydrate metabolism. A deficiency disease in dogs called blacktongue has, since the work of Goldberger and his coworkers in the early twenties, been con

*These pseudo-seborrheic changes should not be confused with seborrheic dermatitis, which is accompanied by oily hair and skin.

Jolliffe, N., Fein, H. D. and Rosenblum, L. A.: Riboflavin Deficiency in Man, New England J. Med. 221: 921-926, 1939.

Finnerud, C. W.: Perlèche: Its Nosologic Status, J.A.M.A. 126: 737-740, 1944.

Jolliffe, N.: The Preventive and Therapeutic Use of Vitamins, J.A.M.A. 129: 613-617, 1945.

Hou, H. C.: Riboflavin Deficiency Among Chinese: Cheilosis and Seborrheic Dermatitis, Chinese M. J. 59: 314, 1941. Abstr. Arch. Dermat. & Syph. 46: 361.

Sydenstricker, V. P., Sebrell, W. H., Cleckley, H. M. and Kruse, H. D.: Ocular Manifestations of Ariboflavinosis, J.A.M.A. 114: 2437-2445, 1940.

Machella, Th. E. and McDonald, P. R.: B-Vitamin in the Human Subject. VI. Failure of Riboflavin Therapy in Patients With the Accepted Picture of Riboflavin-Deficiency. Am. J. M. Sc. 205: 214-223, 1943.

Landor, J. V.: Deficiency of Vitamin B. Lancet 1: 1368-1370, 1939.

Kristensen, K. P. and Vendel, S. V.: Treatment of Eczema With Vitamin B Complex, Lancet 1: 179, 1940.

György, P.: Pediculosis in Rats Kept on Riboflavin-deficient Diet, Proc. Soc. Exper. Biol. & Med. 30: 893, 1933.

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sidered analogous to human pellagra In 1937 Elvehjem discovered that nicotinic acid would cure canine blacktongue Deficiency of nicotinic acid is generally believed to be the main cause of pellagra though clinical pellagra is considered now to be a multiple vitamin deficiency [illegible] which i often associated with symptoms of beriberi [illegible] ariboflavinosis[illegible] (Hou after Ottenstein[illegible]) sprue [illegible] and scurvy

Liver and yeast are the richest natural sources of nicotinic acid Corn contains only about one fifth of the niacin content of wheat and the refined flours of both grains lose almost the entire amount Nevertheless even refined wheat flour still contains three times a much niacin as refined corn flour The peculiar scarcity of niacin in corn accounts for the frequency of pellagra in countries where the diet of the poor consists predominantly of corn flour products The first medical writer on pellagra the Spaniard Casal in 1762, already suspected the use of corn flour in the poor peasant population as one of the causes of pellagra [illegible] We know now that other deficient diets may cause pellagra too Alcoholism and chronic gastro-intestinal disease are the most important *causes of pellagra in countries without endemic pellagra* [illegible] Among 102 cases in Baltimore about one-third were due to alcoholism one-third due to malnutrition and one-third secondary to other diseases.[illegible] Chronic gastric ulcer cancer of the stomach and surgical removal of large parts of the stomach or bowel are conditions which predispose to pellagra [illegible]

The main *centers of endemic pellagra* are found in some warm mediterranean countries and in the southern U.S.A The tropics as well as the cooler climates have only sporadic cases mostly alcoholics, insane or patients with gastric disorders. The incidence has become smaller in the main centers e.g Italy [illegible] (Lavinder after Seale Harris[illegible]) where the morbidity of 104,067 in 1881 had diminished to 55 029 in 1905 probably due to improved living and eating conditions. At the same time the mortality was reduced to about one tenth Thus in the last decades pellagra has become a rare disease in the classical pellagra country A decided trend to the better also prevails in the southeastern U.S.A where the incidence has been reduced by more than 50 per cent from 1929 to 1936 [illegible] Today pellagra is no longer a major public health problem

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[illegible] Sydenstricker V P Geeslin, L E Templeton C M and Weaver J W Riboflavin Deficiency in Human Subjects J A M A 113 1697 1700, 1939

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[illegible] Wheeler G A nd Sebrell W H Control of Pellagra, J A M A 99 95-99, 1932

[illegible] Spies, T D and de Wolf H F Observations on he Etiological Relationship of Severe Alcoholism Pellagra Am J M Sc 186 521-525 1933

[illegible] Easterman, G D and O'Leary P A. Pellagra Secondary t Benign and Carcinomatous Lesions and Dysfunction of he Gastrointestinal Tract Thirteen Cases, Arch Int Med 47 633-640 1931

[illegible] Latrario, A. La pellagre qui disparait en Italie Bull. Office internat d'hyg. pub. 28: 88-136, 1936.

in the Union though it is far from being stamped out. In 1938 3 205 deaths from pellagra occurred mostly in the southeastern states. It is remarkable that the southwest has a very low pellagra rate

The *ages* between 20 and 45 years seem to be most susceptible (Lavinder after J Jadassohn[illegible]) but no age group is immune. Many large statistics show a dominance of the female *sex*. Menstruation pregnancy and lactation are provoking factors The distribution of the lesions suggests strongly that *sunlight* is an important pathogenetic element yet a great number of observations of typical lesions in covered skin (vulva) and of lesions restricted to the typical areas in children who did not wear any clothes prove that exposure to light is not the only provoking factor[illegible] though one of great importance in the eruptive stage[illegible] or after a prolonged deficient diet.[illegible] Some authors even claim a beneficial influence of sunlight in pellagra in some stages[illegible] (for extensive discussion of the sunlight factor see also Seale Harris[illegible])

Lack of a *gastric*, intrinsic anti pellagral factor[illegible] and failure of the liver to store and utilize nicotinic acid are much discussed pathogenetic factors.[illegible]

The *word pellagra* is derived from the Italian *pelle agra* sharp burning skin or from the Latin *pellis aegra* —sick, unhealthy skin. The skin manifestations however though characteristic do not represent the most serious part of the syndrome.

Usually the disease[illegible] *starts* in the spring of the year with increasing lassitude and muscular weakness especially of the legs which make the patients slow moving and resort to the use of canes a suggestive symptom well known to physicians in pellagra regions.

Already in this early stage *burning* of the seemingly still normal skin particularly of the feet, a burning sensation in the throat which cannot be soothed by cold water and other *paresthesias* cause discomfort The patients avoid the heat and lie uncovered in bed Headache and sudden attacks of dizziness or falling without coma convulsions, or nystagmus are typical *nervous symptoms* The reflexes are increased the pupils are small[illegible] Psychoses of widely varying seriousness develop frequently The facial expression of the patient is often a worried fearful melancholic or stuporous one[illegible] Such patients cry easily and are depressed sometimes in realization of the deterioration of *their faculties*. In severe cases hallucinations depression even mania, delirium suicidal at

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tempts and other manifestations of psychoses develop [illegible] On the other hand psychosis with a long confinement to institutions is a predisposing factor to pellagra [illegible]

The internal symptoms are dominated by various phases of inflammation of the *gastrointestinal tract* These disturbances most often account for a fatal outcome [illegible] The oral symptoms will be described later

Anorexia is an early symptom Nausea vomiting and diarrhea are common though greatly varying in intensity Free HCl is absent in more than 66 per cent[illegible] and the pepsin content is low The stools no matter of what consistency are nearly always foul [illegible] *Anemia* is present in about 50 per cent [illegible] *Diabetes insipidus* has been observed frequently Urinary *porphyrin* has been found according to the extent and acuity of the skin manifestations. It is a coproporphyrin which has but a weak light sensitizing effect. Porphyrin excretion was



Fig 395 Pellagra Extensive dermatitis on right hand following accidental unilateral exposure to sunlight From Harris, Seale Clinical Pellagra, The C V Mosby Co)

[illegible]Mietopolsky D Zum Vorkommen pellagroider Erkrankungen bei Alkoholikern und Geisteskranken, Sch rft med W nschr 62: 297-301 1932

[illegible]Chetsen F Klinischer Beitrag zu ken in der Pellagrapsychosen, Ztschr f d ges Neurol Psychiat 148 179-219 1933

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[illegible]Franke G Ueber Pellagra in Irrenanstalten, Psychiat -neurol Wchnschr 35 461-465, 1933.

[illegible]Iabea, M and Mares C Beitrag zum Studium des Magensaftes bei der Pellagra. Der Einfluss des Histamins auf die Achlorhydria der Pellagra, Rev stiint med 19: 2372-2377 1930 Zbl. 59 537

[illegible]Guthrie, J B Achlorhydria in Pellagra, J Trop Med, 36 71 74 1933.

[illegible]Fischer R Das Blutbild bei Pellagra. Folia haemat. 49 146-156, 1933 Zbl. 48 430

[illegible]Turner H Pellagra, Arch. Dermat & Syph. 26 960-963, 1932

[illegible]Rosenthal J A Diabetes insipidus bei Pellagra, Arch f Schiffs- u. Tropen-Hyg. 36 4 1-199, 1933

found negative in the interval between the attacks.[2255] Urinary porphyrin has occasionally been found in alcoholics with or without pellagra.[2256] *Fever* is generally absent but in some cases a spiking fever with diarrhea may create a typhoid-resembling rapidly fatal disease [2257-2258]

Dermadromes.—Skin manifestations of pellagra appear in the majority of the cases.[illegible] They do not cause such dangerous complications as the gastro-intestinal and neurological symptoms but they are of great diagnostic, even pathognomonic importance Together with the sometimes dubious internal complaints they give the syndrome of pellagra its character a a well defined entity



Fig [illegible] —Early pellagrous dermatitis over the patellae (Courtesy Dr Henry Field J and the Upjohn Company

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[2255] Beckh W Ellinger P and Spies T D Porphyrinuria in Pellagra, Quart J Med [illegible] 305-319 1937

[2256] Kark, R and Meiklejohn, A P Pellagra and Porphyrinuria Am J M Sc 201 380-385, 1941

[2257] Ginsburg, D Sporadic Cases of Pellagra in Northern Russia, Sovet vest derm [illegible] 1931 Zbl 41 64

[2258] Margarot, J and Rimbaud, P Typhose pellagreuse Bull Soc Franç de dermat et syph. [illegible] 1261 1264, 1931

The outbreak of typical *pellagral erythema* occurs suddenly sometimes preceded by a premonitory deciduous macular eruption[331] on the dorsa of the hand The true erythema of pellagra appears most frequently at first on the dorsa of the hands In contrast to eczema this lesion is solid and well defined Even in sunlight exposed and tanned forearms the pellagral erythema rarely *extends higher up than the wrist line The palms remain free* The pellagral erythema frequently stops at the knuckles but it may invade the extensor surfaces of the fingers[331]



Fig 207 — Pellagra, collar of Casal (Courtesy Dr M Jessner)

Occasionally the erythema affects the flexor aspects in a strap or cuff like bridge if this occurs it is considered an important diagnostic sign[334] The instep is the site of an additional erythema Here the inflammation extends from a line right above the ankles to the base of the toes. In analogy to the hands the dorsa of the toes are only occasionally involved The erythema may also appear on the face The bridge of the nose is most frequently erythematous, but diffuse or confluent always symmetric patches may occupy the *whole face In the confluent type polycyclic patterns may appear* Facial erythema is more often encountered in women and children than in men and it is often inconspicuous.[334] Narrow bands of skin along the hair line and around



Fig [illegible].—Pellagra Collar of Casal Cheilitis (From Harris, Seale Clinical Pellagra)

the mouth remain normal This mask like distribution is similar to that of chloasma

The fourth typical site of pellagral erythema is a ring of varying width around the entire neck. This is called the necklace or collar of Casal. In the typical instances, Casal s necklace extends into the sternal area as a berloque shaped appendix.

The elbows knees (Bass after Seale Harris[illegible]) shoulders, scrotum, perineum, vulva and infra mammary areas[illegible] are some of the less common sites Sym

[illegible] Costello, M. J Pellagra in Unusual Locations, Arch. Dermat. & Syph. [illegible] 734 1942.

[illegible] Riordan, T. J Gellis, S., and Rubinowitz, A. M. Unusual Sites of Lesions in Pellagra, Arch. Dermat. & Syph. [illegible] [illegible]-684, 1942

metry is a pronounced sometimes astonishing feature [illegible] The skin on which the erythema develops is often slightly edematous At first the erythema consists of confluent pink blotches but within a week it takes on a bright scarlet red color which later has a copper or mahogany hue [illegible]

A few days after the appearance of the erythema the epidermis *cracks and fissures* develop In some cases vesicles blisters pustules and other forms of secondary infection may appear with a predilection for the hair follicles of the dorsa of the fingers. These follicles are often blackened with non-removable

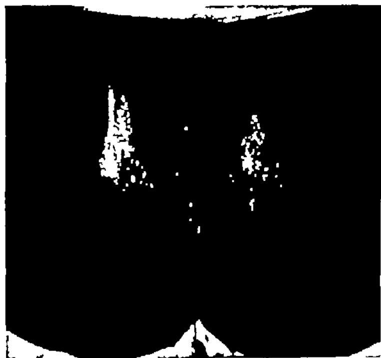


Fig 199 [illegible] pellagra (From Harris, Beale Clinical Pellagra)

di t In the early part of the second week the erythema reaches its peak. A pink halo up to 2 cm in width may surround the lesions. A few days later the acute symptoms recede and ichthyosiform keratosis peeling deep fissuring and increasing pigmentation become the dominating features The pattern of ridges and furrows is coarsened *Follicular keratoses* appear in the erythematous areas On the hands they may be inconspicuous but on the bridge the tip and the sides of the nose and in the *nasolabial folds* they may form grater-like patterns

This follicular hyperkeratosis about the nose has been referred to as sebor rhea [illegible] The facial follicular hyperkeratosis is a frequent and characteristic clinical feature of pellagra [illegible]

The centers of the pellagral areas begin to clear up during the fourth week. The horny layer comes off in large flakes sometimes in sheets of the size of the entire lesion A scaly hyperkeratotic margin may remain for some time.

The typical attack of pellagral erythema is over in 6 to 10 weeks. Pellagra usually occurs in *repeated attacks* mostly in spring and early summer although recurrences in fall occur occasionally. In winter time the patient is usually free of symptoms. The repeated attacks of erythema on the dorsa of the hands leave the skin in an increasingly *atrophic* condition which of course is not reversible.



Fig. 300. Neglected pellagra. Thickened, fissured and pigmented lesions extending far beyond the commonly involved dorsa of the hand. (From Harris, Beale: Clinical Pellagra.)

Longitudinal yellowish stripes (sometimes referred to as striae) are caused by underlying extensor tendons which can be seen through the thin atrophic skin in moderately strong daylight.[211, 225] *Oral manifestations* occur in about one half of the cases (Sandwith after J. Jadassohn[211]). They are important because some of them, e.g., burning and salivation, are among the earliest symptoms. The description of the *tongue* in pellagra vary. Swelling and coating are early



Fig. 201. So-called seborrhea of the nose in pellagra. (From Harris, Beale: Clinical Pellagra.)

symptoms. Denudation may occur on the margins and on the tip while the dorsum remains coated.[211, 224]

In fully developed cases the fungiform papillae may be reddened and swollen (raspberry tongue) or in later stages atrophic, thus giving the appearance of a slick bald thin tongue. Fissures and ulcerations, black hairy tongue, brown coating, ulceration and other lesions have been observed. In acute stages the entire oral mucosa may be fiery red. Aphthous lesions are common.[211]

The *lips* may show small red erosions and there may be angular fissures Plaut Vincent s infection of the gums is a common finding in pellagral stomatitis [illegible]

Vaginitis and vulvitis with much discharge and occasionally edema of the clitoris and labia minora is often called an important or even pathognomonic symptom.



Fig. 302.—Pellagra. Typical dermatitis of the feet and of the patellar regions (From Harris, Seale Clinical Pellagra.)

The *nails* are usually not affected The *hair* is often shed during the attacks and complete alopecia has been seen to develop The loss of the lateral part of the eyebrows is frequent and may have some endocrinological significance (see

[illegible] Kaminsky J and Barova L Zur Klinik der Pellagra in [illegible], Arch f Schiffs-Tropen-Hyg 36 323-336, 1932.

chapter on Endocrines) Of interest is the observation of koilonychia and achylic anemia (Plummer Vinson syndrome) in a woman with pellagra [illegible]

Epithelioma of the skin is a surprisingly rare complication in pellagral dermatitis [illegible]

The occurrence of repeated seasonal attacks has already been mentioned Many *variations in course* and symptomatology have become known so that the diagnosis in nonendemic cases may be extremely difficult or even impossible in the absence of skin manifestation The term *pellagra sine pellagra* is used for such cases Internal symptoms usually precede the erythema for a considerable time [illegible] According to Merck the erythema rarely remains absent longer than one year after the first symptoms Slight erythemas may well pass unnoticed It is probably for this reason that the incidence of dermadromes has in some large series only been 45 per cent [illegible] There is no relationship between the degree of the erythema and the severity of the internal symptoms

Fig 303 Pellagra Typical dermatitis of the dorsal aspects of the hands Fissures and crust (From Harris, Seale Clinical Pellagra)

Of great interest are the *variations of the clinical picture* in various countries and in the same country at different times Thus Casal s necklace and the involvement of the instep areas is relatively common in southern Europe especially the Balkans and rare in the U S A

[illegible] Mellow W Nagelveränderungen bei Pellagra, Arch f Schiffs-u Tropen-Hyg 41 381-383 1937

[illegible] Rutledge W U and Kelly R Epithelioma Secondary to Pellagrous Dermatitis, Arch Dermat & Syph 23 1072-1078 1931

[illegible] Efremow V Etiology Pathogenesis and Prophylaxis of Pellagra Med parazitol i parazit bolez 2 261 276, 1933

The post mortem *pathology* is unrevealing. The most striking feature is the severe hepatic atrophy or fatty degeneration. As can be expected, the skin shows keratosis, parakeratosis, pigmentation and atrophy according to the stage. There is degeneration of the elastic fibers and perivascular infiltration and hyalin degeneration of the vascular walls.[illegible] The unaffected skin also shows hyperkeratosis, atrophy and inflammation, though in a lesser degree.[illegible]

The *diagnosis* is a clinical one since satisfactory laboratory methods have not yet been worked out. One has to consider eczema in which there are no mucosal symptoms and no atrophy, and erythema exudativum multiforme, in which the primary lesion is a coin-shaped erythematous urtica often with a central vesicle. Acrodermatitis atrophicans takes a slow nonseasonal course and has its typical localization, and pityriasis rubra pilaris is nonseasonal and there is no pronounced involvement of the typical pellagra sites although nfacin is reportedly effective.[illegible] The diagnosis of pellagra is easy in endemic and fully



Fig. 304.—Atrophic [illegible] in pellagra. (From H[illegible]ris, Seale: Clinical Pellagra.)

developed cases, but difficult in sporadic and incomplete cases. The typical sites, the sharply outlined lesions, the seasonal attacks, atrophy, nutritional peculiarities including chronic gastrointestinal disease and alcoholism, and the combination of internal and skin manifestations will often assure the diagnosis if its possibility once enters the physician's mind. Incomplete syndromes[illegible] may cause great difficulties in the differentiation from pernicious anemia,[illegible] sprue, Addi-on disease [illegible]nd other entities.

[illegible] Arutiunov, [illegible]: [illegible] zur Erforschung der Pellagra, Diss. [illegible] 1933. [illegible] 457.

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[illegible] Spies, T. D., Payne, W., and Chinn, A. B.: Relationship of Pellagra [illegible] Pernicious Anemia, Proc. Soc. Exper. Biol. & Med. [illegible] 1934.

[illegible] Krjukoff, A.: [illegible] und [illegible] bei [illegible] Fällen von Pellagra, Folia haemat. [illegible] 1931. [illegible]

As a diagnostic sign one has to add successful *treatment* with nicotinic acid[illegible] and a balanced diet. More than one thousand successfully treated cases (nicotinic acid) were reported in 1941 when Seale Harris published his monograph on pellagra. Oral treatment with nicotinic acid in divided doses totaling 500 mg daily supplemented by vitamin B complex and vitamins A, C, D and E, is recommended (Spies e.a. after Gordon and Sevringhaus.[illegible] After a week, 100 mg per day is sufficient. Ruffin and Smith[illegible] advise injections of about 100 mg daily. Injections and larger doses by mouth are followed by flushing of the face together with a feeling of heat and tingling.[illegible] This harmless side-effect can be avoided if the nicotinic acid is given with the meals or replaced by nicotinic acid amide.[illegible]

A high caloric *diet* with the emphasis on meat, liver, eggs, milk and fresh vegetables, removal from slum housing and reduced exposure to sunlight are other important therapeutic factors. Stomach preparations (ventriculin) have been recommended by several authors.[illegible] This medication is based on the discovery of an intrinsic pellagra preventing factor in the gastric juice.[illegible]

The *prognosis* is now better and recovery is often dramatic unless irreversible damage to the nervous and gastrointestinal systems or severe cachexia has developed. In spite of liver diet or medication the mortality in large American series was still 20 to 31[illegible] and even 50 per cent[illegible] 10 years ago but almost zero in private practice.[illegible] With the use of nicotinic acid and other vitamins the mortality has probably been lowered. Many authors stress the importance of prolonged treatment after clinical cure.

The pellagra preventing effect of nicotinic acid has been proved.[illegible]

Pyridoxine has been used with encouraging results in the treatment of adolescent *acne*. The doses varied from 50 to 250 mg daily in divided doses.[illegible] Seborrhea and an acrodynia resembling syndrome have been seen in pyridoxine deficient rats.[illegible]

[illegible] Ruffin, J. M. and Smith, D. T.: Treatment of Pellagra With Special Reference to the Use of Nicotinic Acid, South. M. J. 32: 40-47, 1939.

[illegible] Goldsmith, G. A. and [illegible]: The Vasodilating Effects of Nicotinic Acid, Am. J. M. Sc. 205: 204-208, 1943.

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[illegible] [illegible] Teglbjaerg, H. P.: Neurological Problems in Pellagra, Treatment With Ventriculin, Hospitalstid. 80: 841-8[illegible], 1937.

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[illegible] Jolliffe, N., Rosenblum, L. A. and Sawhill, J.: The Effects of Pyridoxine (Vitamin B_6) on Persistent Adolescent Acne, J. Invest. Dermat. 5: 143-148, 1942.

[illegible] Eckhardt, R. E., György, P. and Johnson, L. V.: Presence of Factor in Blood Which Enhances Bacterial Growth Activity in Relation to Riboflavin, Proc. Soc. Exper. Biol. & Med. 46: 405-408, 1941.

[illegible] Sullivan, M. and Nicholls, J.: Nutritional Approach to Experimental Dermatology: Nutritional Dermatoses in the Rat. II. Vitamin B_6 Deficiency, J. Invest. Dermat. 3: 309-343, 1940.

According to Gordon and Sevringhaus [illegible] pyridoxine is able to heal cheilosis quicker than riboflavin [illegible] Some pellagra cases may heal only after addition of pyridoxine to the other vitamins.[illegible] The healing effect in seborrheic eczema atopic dermatitis and eczema[illegible] still lacks confirmation

No cutaneous manifestations in man have definitely been related to deficiencies of *panthothenic acid choline* and *biotin* Panthothenic acid prevents the greying of the hair in rats fed on a B complex free diet [illegible] A substance in uncooked eggwhite called *avidin*[illegible] is able to inactivate the vitamin *biotin* (vitamin H) Dermatitis of the feet in the chick, and alopecia in rats fed on a diet containing much raw egg white have been observed and some data pointing to analogous phenomena in man are available.[illegible] The so-called egg white injury in the rat has been cured by the addition of excess biotin[illegible] to the eggwhite-rich diet or by inactivating the avidin by cooking *A para-amino benzoic acid* deficient diet causes graying of the fur of rats, which can be cured by feeding this substance [illegible] There is some evidence that repigmentation of gray *hair in man may be stimulated by oral administration of para-amino* benzoic acid or calcium panthothenate The changes produced in some persons were only of theoretical value since in the majority of the cases with any change at all an unsightly yellow or greenish cast was produced sometimes together with scattered wiry black hairs.[illegible] No satisfactory restoration of the hair color which could compete with dying has been accomplished [illegible] Some results of prolonged oral medication with para-amino benzoic acid in vitiligo have been reported.[illegible]

Inositol is required to maintain the fur of the mouse.[illegible] Stryker and Halbeisen[illegible] observed that 32 out of 42 cases of unexplained and noncharacteristic *dermatitis about the neck* and face were accompanied by moderate macrocytic anemia. These cases responded at once to proper diet and liver extract, which in the opinion of the authors was due to the vitamin B complex.

Avitaminosis C—Scurvy.—*Vitamin C or ascorbic acid* occurs in many animal and plant tissues especially in the adrenal cortex from which it was first

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[illegible] Stryker G V and Halbeisen, W A Determination of Macrocytic Anemia as Aid in Diagnosis of Certain Deficiency Dermatoses, Arch Dermat & Syph. 51 116-123 1945

isolated. The human body is unable to synthesize ascorbic acid in the necessary amounts and therefore has to rely on the plant sources especially the citrus fruits peppers green leafy vegetables tomatoes and other plant products

Vitamin C is easily *inactivated* by oxidation Cooking storing without refrigeration alkalization and the presence of copper even in traces rapidly diminish the content of active vitamin C In the organism it is concerned with the maintenance of connective tissue In scorbutic animals *the formation of fibers from fibroblasts is seriously disturbed and the friability of the capillary* walls which in clinical scurvy lead to many manifestations of hemorrhagic disease may be explained by the lack of adequate intercellular substances [illegible]

Scurvy is at the present time a rare disease In adults it is seen following malnutrition among inmates of ill-managed prisons or other institutions in times of famine or after prolonged gastrointestinal disease with restricted diet. Scurvy is more frequent in infants fed on cow's milk especially if the milk is being sterilized by boiling

In adults general weakness pain in the legs gingivitis purpura and other hemorrhagic symptoms are the classic manifestations Undeveloped cases are supposedly common and often mistaken for rheumatism [illegible] Infantile scurvy is clinically characterized by pallor a worried facial expression drawn up legs in bed crying when handled pain in the legs subperiosteal hemorrhages especially in the epiphyseal region and gingivitis with bleeding if the child already has teeth Anorexia loss of weight susceptibility to infection fever intestinal disorders hematuria and epistaxis are other symptoms. Urbach[14] considers the saturation test for vitamin A deficiency as much more valuable than single determinations of the vitamin A content of blood plasma and urine This test is based on the observation that the ascorbic acid levels in blood and urine fail to rise substantially and for considerable time in a vitamin A depleted organism after the intravenous injection of 500 mg of ascorbic acid In the normal 40 per cent of the injected vitamin is excreted within four hours while in scurvy the excretion is trifling 20 per cent at the most The diagnosis is helped by the positive tourniquet (Leede-Rumpel) test or a similar method[2277] for testing the fragility of the capillaries. Bleeding and coagulation times as well as blood platelet count are normal

The blood picture is normal except for a moderate anemia

The dermadromes of scurvy are significant, though not specific The follicular slightly papular dull red hemorrhagic *rash* occurs early in the course of clinical scurvy Later many of these papules show pronounced intrafollicular keratosis The rash is symmetrical and occupies predominantly the extensor surfaces of the extremities particularly of the lower legs and the hairy region of the trunk The palms and soles the face and the scalp remain free [illegible] Some of the follicular lesions are truly petechial without a papular character Large subcutaneous extravasations occur in the parts which are subject to friction and

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[2276] Eddy W H The Avitaminoses, Baltimore 1937 Williams & Wilkins Co

[2277] Göthlin, G F Method for Determining Strength of the Skin Capillaries Indirect Estimation of the Individual Vitamin C Standard. J Lab & Clin Med 18:4 [illegible] 1933

trauma such as the popliteal areas and the scalp Extravasation beneath the conjunctivae also occurs These dermadromes are more common in infantile scurvy (Möller Barlow disease)

The papulo-hemorrhagic, keratotic and follicular rash in scurvy has for a long time been known under various other names, like lichen scorbuticus [illegible] lichen pilaris or scorbutic gooseflesh [illegible] The First World War gave the opportunity for new observations of scurvy on a large scale. In some series the papulokeratotic rash was present in 87 per cent.[illegible] The follicular keratoses often affected almost all follicles especially of the anterior aspects of the legs so that a grater-like surface resulted *Microscopic* features of the scorbutic skin lesions are capillary congestion interstitial hemorrhage and edema without inflammatory infiltrate The follicle contains a plug formed of the remnant of the hair and keratotic material The hair roots are not destroyed

The follicular lesions in scurvy (Whitfield after Wiltshire[illegible]) have much clinical resemblance to those in vitamin A deficiency However the vascular factor which is so pronounced in scurvy is lacking in phrynoderma Scheer and Kell [illegible] therefore believe that the follicular keratoses in scurvy are not due to a multiple deficiency In *experimental vitamin A* deficiency in man follicular keratotic papules and perifollicular petechiae were among the first symptoms.[illegible] Ecchymoses and gingivitis followed

Hyperpigmentation in scurvy has been observed[illegible] although it is not yet sure whether it is due only to hemosiderin from the hemorrhagic disease or also to the increased melanin production under the influence of vitamin C deficiency Ascorbic acid is able at least under experimental conditions to prevent melanin formation (von Szent-Györgi after Schauff[illegible]) In the human skin melanin occurs associated with vitamin C [illegible]

Gingivitis in scurvy being an early signal is of great significance. The gums are swollen and bleeding the papillae being enlarged In small children the teeth may become submerged under the swollen gingiva. If the scurvy lasts longer the teeth may fall out and the alveolus may become necrotic. It has often been stated that scorbutic gingivitis does not develop in an edentulous mouth

The *healing of wounds* is greatly impaired in scurvy[illegible] at least in part due to the disturbed production of intercellular substances.

Untreated and fully developed scurvy is a disease with a high mortality However if treatment with 200-300 mg of vitamin C is administered daily either orally or parenterally together with a full diet surprising recovery may be seen Gordon and Sevringhaus[illegible] state that in all the field of medicine there is probably no more dramatic or gratifying result from a therapeutic measure than that which occurs when a patient with scurvy is given an adequate amount of ascorbic acid

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[illegible] Jessner S. Hautanomalien bei inneren Krankheiten, Berlin, 1903 A Hirschwald.

[illegible] Scheer M and Keil, H. Follicular Lesions in Vitamin A and C Deficiencies, Arch. Dermat. & Syph 30: 177 184, 1934

[illegible] Wiltshire H Hyperkeratosis of the Hair Follicles in Scurvy Lancet 2: 564 1919

[illegible] Crandon, J H Lund, C C and Dill, D B. Experimental Human Scurvy New England J Med 223 353-369, 1940.

[illegible] Bartlett, M. K., Jones, C M., and Ryan, A. E Vitamin C and Wound Healing Experimental Wounds in Guinea Pigs, New England J Med 226: 469-473, 1942

No relationship between the level of vitamin C in the blood and the development of a *variety of skin diseases* altogether 181 cases was found[illegible] and no curative effect was noticed.[illegible] Effects on *colloid milium*[illegible] and on *toxicodermas* from arsphenamine,[illegible] mercury,[illegible] gold[illegible] have been reported. Some evidence is available that vitamin C exerts a detoxifying influence on arsphenamine treatment and thus may be able to prevent toxic reactions.[illegible]

[illegible] Lever, W. F. and Talbott, J. H.: *Role of Vitamin C in Cutaneous Diseases*, Arch. Dermat. & Syph. 41: 657-663, 1940.

[illegible] Hansen, P. and Braestrup, P.: Vitamin C and Skin Diseases. Acta dermat.-venereol. 20: 676, 1939. Abst. Arch. Dermat. & Syph. 41: 709.

[illegible] W[illegible] y, R. C.: Colloid Milium: Vitamin Deficiency? Arch. Dermat. & Syph. 45: 1148-1155, 1942.

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Chapter XXXII

DISORDERS OF THE BLOOD AND BLOOD FORMING ORGANS

(Lymphoblastomas and Allied Disorders)

Leukemia lymphosarcoma Hodgkin's disease, mycosis fungoides, and the subvarieties of these disorders are now—at least in America—commonly grouped together under the name of lymphoblastomas.[illegible] This term which is not much used in other countries is based on the conception that all these diseases have tumorlike features and that they are related by a common characteristic cell the lymphoblast or a derivative of this cell. A great number of transitional cases have been described to corroborate the close relationship.[illegible] The neoplastic features are found in the continuous and uncontrolled proliferation of cells, which tend to differentiate like their cells of origin The proliferation is infiltrating and is devoid of an orderly structural arrangement. No cause is known The course is invariably fatal no certain phenomena of immunity or protection are known.[illegible] Heredity plays a role.[illegible]

Other authors[illegible] produced some evidence for the infectious nature of the group. Spread of the disease from a portal in the lymphatic tissues of the gastro-intestinal and respiratory tract inflammation necrosis, fever and some experimental facts can be interpreted in favor of an infectious, possibly virus[illegible] etiology Possibly in future a conception of infectious neoplasm will evolve

The term lymphoblastoma as a generic term has been accepted by authors who do not approve of the merging of the entities in question since they consider the differentiating characteristics of greater importance.[illegible]

Leukemia[illegible]

Leukemia is a fatal disease of unknown etiology primarily involving the blood-forming organs i.e the bone marrow the spleen the lymphatic nodes

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[illegible] Ormsby O S and Finnerud, C W Mycosis Fungoides, Arch Derma & Syph 27: 631-642 1933

[illegible] Haden R L Hematology Philadelphia, 1939, Lea & Febiger

[illegible] Rosenthal, N and Harris, W Leukemia, Diagnosis and Treatment J A M A 104 702-706, 1935

and the reticuloendothelial cell. It is characterized by widespread rapid and disorderly proliferation of the white blood cells and their precursors. Almost without exception either during the entire course or in some phase of the disease the white blood count is high, sometimes very high. The appearance of immature leukocytes in the blood, often in very large numbers, is particularly significant. This proliferation of white cells almost always involves only one of the three types, the lymphocytes, the granulocytes or the monocytes. This is surprising considering the adjacency of the mother cell in the bone marrow and in other organs. The resulting three main types of leukemia, the lymphoid, the myeloid and the monocytic, are clinically quite different. Generalized enlargement of the lymph nodes is typical of lymphoid leukemia, but some lymphadenopathy may be present in the other types. The spleen is usually enlarged, the very large sizes being found in myeloid leukemia. In monocytic leukemia gangrenous and hemorrhagic lesions of the mucous membranes often dominate the picture. Weakness, *dyspnea, fever and anemia occur in all types. A hemorrhagic tendency is an early and common feature in all types. The metabolic rate is frequently increased.* In two out of three cases the disease takes a chronic course over years with or without remissions. The acute disease ends fatally in a few weeks or months, often with hemorrhagic and mucosal symptoms. Acute course is known to occur in any of the three types. Approximately one half of the myelocytic and of the monocytic cases but only one fourth of the lymphocytic cases are acute.[illegible]

The leukemias are relatively rare diseases. They constitute a little more than one-half per cent of the necropsy diagnoses in a large American series (Ikeda after Forkner[illegible]) with about two cases of lymphoid leukemia to one case of myeloid leukemia. This ratio among the necropsies differs materially from that of hospital admissions. Among 455 cases of leukemia treated in Mount Sinai Hospital in New York, roughly 66 per cent were myeloid, 28 per cent lymphoid and 1.5 per cent monocytic. In Denmark roughly one out of 50 000 persons dies of leukemia per year (Nielsen after Forkner[illegible]). No age is exempt but the fourth decade of life has the largest incidence. The male patients outnumber the females two to one.[illegible]

Dermadromes Especially of Lymphatic Leukemia.—Cutaneous lesions occur in all types of leukemia. It is customary to distinguish between specific skin lesions which histologically consist of the same cells which are characteristic of the blood in the case in question and nonspecific dermatoses which *are often seen in leukemia but do not contain leukemic elements.*

The border line is not very sharp since originally nonspecific lesions may finally become pervaded by the leukemic cells. Even grossly normal skin may prove to harbour specific infiltration. The nonspecific group is often called leukemids[illegible] or just ids. The term leukemid has become misleading since

[illegible] Friedmann, A. B. and Meyer, L. M.: Observations on Over 100 Cases of Myelogenous and Lymphatic Leukemia, Radiology 44: 341-343, 1945.

[illegible] Audry, C.: Sur les leucémides, Bull. Soc. franç. de dermat. et syph. 13: 116-121, 1902.

in analogy to the "ids" in infections it suggests the specific and not the non-specific type e.g. syphilids trichophytids, etc. (see discussion to Sweitzer[illegible]) The term "accompanying dermatoses" (Hautbegleiterscheinungen[illegible]) has not found approval in the Anglo-Saxon literature. The adjective, toxic, has also been used to characterize these dermatoses. It implies an etiology which has not been proved. It seems best to speak of specific and nonspecific dermadromes. There is no dermadrome which in a clinical sense is absolutely characteristic of one or the other types of leukemia. The majority of published cases of skin lesions belongs to the chronic lymphoid leukemia.[illegible] However in an analysis of the cutaneous aspect of 160 cases of leukemia[illegible] the incidence was about equal in both main types. Specific infiltrations were more common in lymphoid leukemia (8.3 versus 5.5 per cent). The cutaneous involvement in monocytic leukemia seems very high (75 per cent) but only small numbers are so far available. The diagnostic difficulties in skin leukemia are considerably increased by the experience that the cases with leukemic skin manifestations are frequently subleukemic or aleukemic in the blood.[illegible] They often show a leukemic blood only in late stages of the disease. Another difficulty may be created by lymphocytomas. These are infiltrations or tumors which histologically resemble leukemia but remain localized.

Non-Specific Dermadromes.—These are variable. In their monograph Arzt and Fuhs[illegible] mention dermatitis, eczema, erythema exudativum multiforme, urticaria, purpura and bullous and rupial eruptions. This coincides with Nanta's remark that there are so many combinations in this group that if one would like to go into grouping every single observation could represent a type of its own. The incidence is probably higher than fifty per cent, minor skin lesions often passing unnoticed or at least unrecorded in the medical wards. Pruritus for instance sometimes without any visible skin changes, which seems to be the most common symptom, was recorded only in three per cent of the leukemia cases of Epstein and MacEachern.[illegible] Most authors agree that severe itching alone or in connection with visible rashes is a frequent symptom.[illegible]

Purpura of varying degrees is also common in leukemia. In large series[illegible] it exceeds the other leukemic rashes. This is not surprising in view of the thrombopenia and hemorrhagic tendency in the leukemias. Chronic urticaria[illegible] has quite often been described. It is related to Buschke's prurigo lymphatica. This is a violently itching widespread not too dense eruption of small papules, which soon become scratched and crusty or impetiginous. The lesions may form

[illegible]Sweitzer, S. E. Leukemid. Arch. Dermat. & Syph. 29: 1083-1093, 1934.
[illegible]Oettgen, H. Zur Leukämie der Haut. Med. Klin. 33: 872-877; 404-406, 1937.
[illegible]Epstein, E. and MacEachern, K. Dermatologic Manifestations of the Lymphoblastoma-Leukemia Group. Arch. Int. Med. 60: 867-878, 1937.
[illegible]Arzt, L., and Fuhs, H. Hauterkrankungen bei Leukosen und Leukoblastomen sowie verwandten Zuständen, Handb. d. H. u. Gk. 8, 1 1928.
[illegible]Cornbleet, T. and Murphy, E. L. Lymphatic Leukemia (Chronic) Leukemia Cutis. Arch. Dermat. & Syph. 36: 643-645, 1937.
[illegible]Cavanaugh, J. M. Lymphoblastoma. Arch. Dermat. & Syph. 23: 887, 1931.
[illegible]Schreiner, C. H. Ein Fall von chronischer lymphatischer Leukämie ohne Milz oder Mandelgeschwulst, aber mit Urticaria. Med. Rev. 53: 430-432, 1936; Ibid. 53: 548.
[illegible]Orland, A. Osservazione [illegible] leucemico. Arch. ital. di dermat. sif. 7: 397-411, 1931; Ibid. 47: 92.

small erosions and ulcers which leave pigmented spots and streaks. Thus a mottled melanoderma may ensue which resembles the so-called vagabond's skin. The frequent loss of body hair in this stage is not only due to the rubbing off but also to a beginning specific infiltration around the hair follicles.[illegible] Total alopecia has been observed. The histologic picture is, as a rule, not a typical leukemic one, but surprising specific findings have become known, demonstrating that there is no sharp borderline between the specific and nonspecific dermadromes.[illegible] The same is true of the herpes zoster which occurs quite often in the course of leukemia.[illegible] While the zoster may take a normal course, its scars may later become the sites of specific leukemic infiltrations.[illegible] Such provocations of specific leukemic lesions by local inflammation or trauma, interpreted as Koebner's phenomenon, have been observed in many cases after local trauma like insect bites, burns, cupping, piercing of the earlobe, punching of the ear, and other local mechanical injuries.[illegible] Aberrant or generalized zoster eruptions, which are quite rare, seem to occur more frequently in leukemia.[illegible] The rare connection of zoster and chicken pox in adults, and also the varicelliform eruptions (H. R. Foerster in discussion to Barney[illegible]) have been observed several times in leukemic patients. The generalization of zoster seems to occur especially in persons whose resistance has been weakened by disease or age.[illegible] Evidence of involvement of the corresponding spinal ganglion by hemorrhage or leukemic infiltration is on record.[illegible] Some of the zoster eruptions in leukemia may have been caused by arsenicals.

Specific Leukemic Dermadromes.—Specific leukemic dermadromes appear in several types which, notwithstanding their different clinical aspect, have

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[illegible] Nanta, A.: Les troubles de l'appareil hématopoïétique (Hématodermies), Nouvelle Pratique Dermatologique, vol. 5, pp. 421-461.

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[illegible] Bertaccini, G.: Ueber eine noch nicht beschriebene Hauterscheinung (Rupia) im Verlauf einer chronischen leukämischen Lymphadenose, Derm. Wchnschr. 98: 741-745, 1934.

[illegible] Craver, L. F., and Haagensen, C. D.: A Note on the Occurrence of Herpes Zoster in Hodgkin's Disease, Lymphosarcoma and the Leukemias, Am. J. Cancer 16: 502-514, 1932.

[illegible] Jadassohn, J., II: Leukämie in Zoster-Resten, Zbl. 33: 17.

[illegible] Jadassohn, J.: Herpes Zoster und varicellenartiges Exanthem bei lymphatischer Leukämie, Zbl. 39: 83.

[illegible] Halle, H.: Zoster und Leukämie. Provokation leukämischer Infiltrate in der Haut, Arch. f. Dermat. u. Syph. 160: 234-24[illegible], 1930.

[illegible] Ku[illegible], F.: Zoster bei Leukämie, Arch. f. Dermat. u. Syph. 164: 441-461, 1932.

[illegible] Ferreira Marques, J.: Herpes zoster generalisatus bei Leukämie, Arch. f. Dermat. u. Syph. 176: 295-30[illegible], 1937.

[illegible] Gottron, H., and Jacobi, H.: Subleukämische Lymphadenosis cutis nach Herpes Zoster generalisatus, Zbl. 32: 84, 1930.

[illegible] Barney, R. E.: Leukemia Cutis Resembling Herpes Zoster, Arch. Dermat. & Syph. 25: 1150-1151, 1932.

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[illegible] Haack, K.: Zoster generalisatus bei lymphatischer Leukämie, Dermat. Wchnschr. 96: 1519-1520, 1933.

[illegible] Barton, R. L., and O'Leary, P. A.: Herpes Zoster Generalisatus Associated With Chronic Lymphatic Leukemia, Arch. Dermat. & Syph. 31: 203-205, 1935.

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[illegible] Philadelphy, A., and Fuhrbofer, L.: Varicellen bei leukämischer Lymphadenose, Arch. f. Dermat. u. Syph. 160: 312-316, 1930.

[illegible] Freund, H.: Zoster und Leukämie, Arch. f. Dermat. u. Syph. 164: 470-480, 1932.

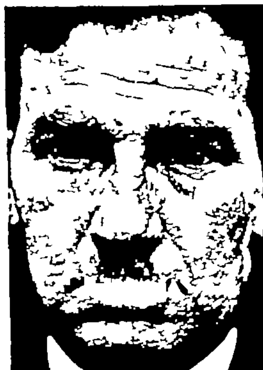


Fig. 303 —Lymphatic leukemia. Specific papular eruption. (Courtesy Dr M Jessner)

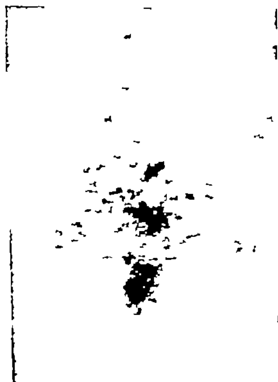


Fig 304 L mphatic leukemia lichenoid eruption [illegible]ourtesy Dr [illegible] Jessner

a common histopathology the leukemic infiltration The rarest of the specific leukemic involvements of the skin is the generalized papular rash which has great similarity to a secondary syphilitic exanthema The *dense*[1330] *eruption of* small red mostly follicular papules favors the trunk especially the hips leaving the face and the limbs relatively free Considering its great rarity the diagnosis



Fig 307 Specific papular eruption in lymphatic leukemia (Courtesy Division of Dermatology Department of Medicine University of Chicago)

of leukemia will hardly be made from the rash alone But after exclusion of syphilis and other papular exanthemas, e.g drug eruptions leukemia should be considered[1330,1331] This diagnosis will be much easier if the papules tend to coalesce and form plaques or if some papules reach tumor size *Such cases of* tumors arising from beds of papules link the papular type of cutaneous leukemia with the leukemic tumors. Another transition is the furunculosis-resembling rash of large not very distinct papules of moderately dense distribution[22]

The *cutaneous tumors* in leukemia[1331,433] have been seen in sizes varying from a pinhead to a large potato They are oval or round mostly raised. If they are

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[1330] Arzt, L. Prurigo Lymphatica, Zbl 84 71

[1331] [illegible] Lymphatische Leukämie mit spezifisch papulösem Exanthem und bullöser Eruption, Zbl. 81: 84

confluent the lines of coalescence are sometimes recognizable by deep linear grooves. Their color may be red bluish purple brown even almost black. Under diascopic pressure they appear brown. The skin over the tumors may be extended glossy atrophic with some telangiectases or scaly. The tumors are usually movable. The small tumors are quite hard. The large growths are often described as soft, less often as having the elastic hardness of cartilage. The tendency to spontaneous regression either by central necrosis or healing with atrophy is small (Freudenthal after Gottron[illegible]) also[illegible]. They are almost always painless. The tumors may appear in any region of the body surfaces



Fig [illegible] — Lymphatic leukemic tumors (Courtesy Dr. M. Jessner)

but they have a definite affinity to the soft acra of the face i. e. the eyelids, the lips the nose the cheeks, and the ear lobes. There is a certain tendency to symmetric development. Such symmetric tumors may create the most grotesque disfigurement of the human face known to medicine. In such rare but well known cases large bluish bulges hang over the eyes and cheeks obstructing the vision. The nose resembles a proboscis, the ear lobules may be pendulous and elongated. In other cases the tumefaction is more diffuse over the face resulting in a facies leonina not unlike leprosy. The scalp may also be involved. The penis and praeputium sometimes become the site of leukemic tumors which may seriously interfere with micturition. The nipples soft acra too have several times been described as a characteristic site of leukemic tumors.[illegible]

[illegible] Bechet, P. E. Leukemia, Arch. Dermat. & Syph. 18: 600, 1928
[illegible] Schildkraut, J. M. Circumscribed Leukemia Cutis, Arch. Dermat. & Syph. [illegible]: 144 [illegible]
[illegible] Whitehouse Myelogenous Leukemia, Arch. Dermat. & Syph. 18: [illegible], 1928

The *mucous membranes* of the mouth pharynx larynx nose and eyes may also become involved Oral lesions of this kind are described as nodular or diffuse infiltration A picture of a patient of Milian's[illegible] shows a lobulated gyrate tumor involving the whole soft palate and covered with petechiae Such infiltrations of the soft palate have been seen several times[illegible] Connor describes a similar case in a Negro There were large flat granulomatous masses practically covering the buccal surfaces on both sides Smaller tumors were located on the soft palate and on the gums. The masses were dull red the edges overhanging the bases sessile There was some superficial ulceration in this case but the lack of ulceration is emphasized in other cases In other instances[illegible] the infiltrations were smooth and multiple scattered over the entire mucosa of the upper air passages from the lips down to the larynx. In one case a tumor of the epiglottis accompanied by skin tumors proved to be of lymphocytic origin[illegible]

Tumors have been observed in all ages including a seven months old baby[illegible] a three year-old boy[illegible] and very old people

The tumors often grow slowly or remain stationary over long periods even as long as thirteen years

In some cases the appearance[illegible] of cutaneous tumors coincides with a change of a chronic course to an acute phase of leukemia with more numerous immature cells in the blood[illegible]

The diagnosis of the leukemic tumors is easy in fully developed cases But difficulties which can only be overcome by repeated biopsies may arise if there is only one small nodule[illegible] or if the lesion resembles other tumors e g ulcerated epithelioma[illegible] melanoma[illegible] hemangioma[illegible] or neurogenic sarcoma (author's case) Blood count and biopsy will finally assure the diagnosis but it should be remembered that large tumors of the skin may be found in an aleukemic phase of the disease[illegible]

Generalized Exfoliative Erythroderma This complication of leukemia is very rare Epstein and MacEachern[illegible] saw one case in 60 cases of chronic lymphoid leukemia and not a single case in 90 cases of myeloid leukemia It is about five times rarer than the other dermadromes of lymphoid leukemia

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[illegible] Theodorescu and Mahler A Lymphatische Leukämie mit Hauterscheinungen, Zb 40 402 1931

[illegible] Marx H Leucaemia cutis mit Beteiligung des Rachens und des Kehlkopfes, Ztschr f Laryng Rhl 19 207 209 1930

[illegible] M Caffert Lymphoma, Arch Dermat & Syph 19 [illegible] 1929

[illegible] Halling-Ach ab J B Ein Fall von Haut[illegible] und myeloide Reaktion im Blu[illegible] Nederl. tijdschr geneesk 1[illegible] 719-720 1930 Zbl 35 [illegible]

[illegible] Semon H Leukemia Cutis Proc Roy Soc Med 23 1031 1032, 1930

[illegible] Emile-Weil P and Isch-Wall P Les leucémies & [illegible] Sang 5 415-429, 1931

[illegible] Zeisler E P and Caro M R Lymphatic Leukemia of the Skin Arch Dermat & Syph 26 523 1932

[illegible] Buschke A Lymphatische Leukämie, Zbl 41 395

[illegible] White C J Leukemia Cutis, Resembling Epithelioma, Arch Dermat & Syph 26 431 1932

[illegible] Gray A M H Leukemia cutis Proc Roy Soc Med 23 1041 1042 1930

[illegible] Rostenberg A Lymphatic Leukemia, Arch Dermat & Syph 23 867 1931

[illegible] Throne B Lymphatic Leukemia, Arch Dermat & Syph 20 566, 1929

[illegible] Zimmerman E F and Curtis, H C Aleukemic Myelosis With Cutaneous Nodules, Arch. Dermat. & Syph 22 674-681 1930

The condition may precede the blood changes for years[illegible] or it may develop in any stage of the leukemic process. It may develop secondarily to a specific papular rash or specific nodules,[illegible] or nodules or tumors may follow the diffuse reddening of the skin.[illegible] In other cases the universal involvement of the skin was ushered in by swelling and erythema of some regions, mostly the groin and armpits,[illegible] or by bullous eruptions suggesting pemphigus.[illegible] In some instances excessive perspiration was an initial symptom.[illegible] Pruritus was almost always severe and remained so throughout the course of the disease. The variety of pictures seen in the initial stage of the disorder is in remarkable contrast to the uniformity of the later stages.

The entire body surface is red, sometimes bright red, sometimes dusky or purplish. The skin is often thick and leathery, hardly pliable. While the small wrinkles are *mostly flattened, the large folds are the more deepened. The loss* of pliability expresses itself in painful fissures, especially on the hands. The exfoliation varies from slight branny scaling to the shedding of large sheets of dry epidermis. In some cases vesicles, crusts and oozing create the impression of a generalized eczema. Nodules or plaques are sometimes found in the erythroderma. The axillary and pubic hair is shed early or rubbed off; the hair of the bearded area and of the scalp follow.[illegible] The ground off concave edges of the nails and their glossy surfaces, tell of constant rubbing and scratching. Later on they are often dystrophic, thickened, opaque, brittle and discolored.

The superficial lymphatic nodes are all swollen, the lack of axillary and pubic hair making them more visible. The patient is very uncomfortable. The rhagades, the pruritus, the ectropion which usually develops, complicating pyodermic infections, chilliness and the weakness and depression caused by the severe disease create a horrible syndrome of suffering. The course may drag on over many years. In the later stages the infiltrated skin may become atrophic.[illegible] Leukemic erythroderma is usually not influenced by any treatment, including radiation.

The fatal outcome is frequently precipitated by bronchopneumonia.

[illegible] Cerbin, J. B. and Trieto, J. O.: Erythrodermische Form der aleukämischen Myelose, Actas dermo-sif. [illegible] 316-323 [illegible] 1937. Zbl. [illegible] 70.

[illegible] Fuhrmann, J.: Erythroderma leucaemicum als chronischer lymphoider Leukämie mit Knötchen nach Röntgenbestrahlung en[illegible] Orvosi hetil. 77: 304-307 [illegible] Zbl. 48: 400.

[illegible] Brebari, E.: Eritrodermia lymphatica [illegible] Bull. Soc. Region. Soc. Ital. Dermat. pp. 110-116, 1932.

[illegible] Dalina, L. and De Marval, L.: Ueber einen Fall von Erythrodermie und akuter lymphatischer Leukämie. Derm. Wchnschr. [illegible] II: 1180-1187.

[illegible] Michelson, H. E.: Leukemia Cutis, Arch. Dermat. & Syph. 22: 148-149, 1930.

[illegible] McCarthy, F. P.: Raynaud Disease (Possibly Due to Chronic Arsenic Poisoning), Arch. Dermat. & Syph. 23: 787-788, 1931.

[illegible] Margarot, J., Rimbaud, P. and Roche, J.: *Érythrodermie constituant la manifestation clinique initiale et pendant quelque temps exclusive d'une leucémie. Éléments primordiaux et d'[illegible]* Bull. Soc. franç. de dermat. et syph. 42: 1803-1810, 1935.

[illegible] MacCormac, H.: Leukaemic Erythroderma. Proc. Roy. Soc. Med. 31: 1171-1174, 1938.

[illegible] Arnstejn, P. T.: Chronische lymphatische Leukämie mit Lymphomen der Haut. Serb. Arch. f. d. ges. Med. 30: 413-417, 1928. Zbl. 28: 298.

[illegible] Theodoresco, S.: Sur un cas d'érythrodermie leucémique. Bull. Soc. roum. Derma. 1: 61-64, 1929. Zbl. 31: 332.

Chronic Myeloid Leukemia.—Skin manifestations of chronic myeloid leukemia being much rarer than those in lymphoid leukemia are not yet well enough known to insure a definite type. Hardly more than fifty cases have been published. All the dermadromes observed in chronic lymphatic leukemia have been seen in the chronic myeloid type too. Nonspecific hemorrhagic,[illegible]



Fig. 309 Fig. 310

Fig. 309.—Chronic myeloid leukemia. Specific cutaneous tumors. (From Paul, J. T. and Limarzi, L. R. Arch. Dermat. 1942.)

Fig. 310. Chronic myeloid leukemia. (From Paul, J. T. and Limarzi, L. R. Arch. Dermat., 1942.)

urticarial, pruriginous rashes,[illegible] as well as infiltrations, plaques,[illegible] and tumors are known.[illegible] The impression prevails that there is less tendency for the tumors to develop in the soft acra, especially in those of the face. The facies leonina which is so striking in some cases of lymphoid leukemia has not yet become known in myeloid leukemia. The tumors seem to occur more frequently on the trunk.[illegible] The extremities have only occasionally been found to be involved.

[illegible] Martenstein, H. Multiple Hautblutungen bei myeloischer Leukämie. Zbl. [illegible] 1937.

[illegible] Nekam, L. Les manifestations cutanées de la leucémie myéloïde chronique. Bull. Soc. franç. de dermat. et syph. 44: 1236-1254, 1937.

[illegible] Haden, R. L. Leukemia Cutis (Myeloblastic). Arch. Dermat. & Syph. 37: 870-871, 1938.

[illegible] Paul, J. T. and Limarzi, L. R. Specific Cutaneous Lesions in Chronic Leukemia. Arch. Dermat. & Syph. 45: [illegible], 1942.

(Aubertin's case in a picture shown by Nanta[2314] Hollander[2264] and others.) Telangiectases on and around the tumors are especially mentioned by various authors.[2269,2256]

There seems to be a more marked tendency to hemorrhage necrosis and ulceration in the myeloid tumors particularly in those of the mouth[2269,2264] than in the corresponding lymphoid lesions.



Fig. 311 – Chronic myeloid leukemia. Specific infiltration surrounding sweat gland (From Paul J T and Lizzard, L. R Arch. Dermat 1942.)

Monocytic Leukemia —Monocytic leukemia[2267] constitutes only a small fraction of the leukemias.[2268,2269,2261] But it is likely that cutaneous and oral involvement is relatively frequent in this type (three out of four cases of the series of Epstein and MacEachern[2244])

While so far no specific clinical picture different from the other leukemic dermadromes has evolved the frequent occurrence of exfoliative dermatitis is remarkable Purpuric and bullous lesions are often encountered in early stages and so are indurated eczematoid plaques resembling the premycotic stages of

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[illegible] Hollander L, Kastlin, G J, Permar H H and Schmitt, C L Myeloid Leukemia With Cutaneous Manifestations, Arch Derm & Syph. 29 821-834, 1934

[illegible] Richter W Myeloische Leukämie mit Hautmetastasen unter dem Bilde eines Abscesses, Zbl 44 372

[illegible] Oet ron, H Perakute Myeloblastenleukämie Zbl. [illegible] 466, 1931 1932.

[illegible] Schilling, V Seltene akut Leukämieformen, Verhandl. 37 Kong. deutsch. Ges. inn. Med Wiesbaden 925

[illegible] Doan, C A and Wiseman, B K Monocyte, Monocytosis, and Monocytic Leukosis, Ann. Int Med 8 383-416, 193

mycosis fungoides. Shotty papular, nodular or tumorous, discrete or coalescent eruptions have become known. The lesions may be either superficial or deep seated, creating sarcoid pictures. Their development seems to be faster and their tendency to spontaneous regression more marked than in the other leukemic tumors. Ulceration is considered ominous. As in the other leukemias the cutaneous changes may precede, accompany or follow the



Fig. 313.—Monocytic leukemia. (Courtesy Division of Dermatology, Department of Medicine, University of Chicago.)

blood changes. The dermatological diagnosis of monocytic leukemia can only be established by biopsy and in connection with other clinical findings, since the cutaneous picture may resemble all other lymphoblastomas.

Loveman, A. B.: Monocytic Leukemia Cutis, South. M. J. 29: 257-264, 1936.

Montgomery, H., and Watkins, C. H.: Exfoliative Dermatitis as Manifestation of Monocytic Leukemia Schilling, Minnesota Med. 22: 636-641, 1939.

Mercer, S. T.: The Dermatosis of Monocytic Leukemia, Arch. Dermat. & Syph. 31: 615-634, 1935.

Freeman, H. E., and Koletsky, S.: Cutaneous Lesions in Monocytic Leukemia, 2 Cases, Arch. Dermat. & Syph. 40: 218-240, 1939.

Lynch, F. W.: Cutaneous Lesions Associated With Monocytic Leukemia and Reticulo-Endotheliosis, Arch. Dermat. & Syph. 34: 775-796, 1936.

Chloroma.—In contrast to the earlier literature chloroma is now considered a variant of myeloid leukemia originating from the marrow especially of the cranial bones, and taking the course of a highly malignant tumor The name (green tumor) characterizes the green color of the lesions produced by a lipid, probably iron-containing substance. Two main clinical types of chloroma occur[illegible] In the juvenile cases a rapidly growing orbital tumor produces exophthalmus and finally profound proptosis. Cranial tumefaction with a great variety of symptoms, lymphadenopathy gross invo vement of other bones and severe anemia follow In the much rarer adult type the course resembles acute leukemia complicated by gross bony involvement

Since the arrival of the modern methods of hematology myeloid leukemia has been found to be present almost constantly Autopsy reveals green foci of myeloid tissue throughout the body

Severe anemia with a green hue and petechial purpura and varying macular or papular rashes[illegible] and tumors[illegible] have been described mostly in children Dense nodular greenish rashes in adults are known Similar to other acute leukemias, ulcerative gingivitis and easily bleeding infiltrations of the base of the tongue and of the tonsils occur In contrast to the oral lesions of other leukemias these lesions are green in color



Fig. 518 — Ecchymoses in acute lymphatic leukemia

Acute Leukemia —Acute leukemia occurs about half as often as chronic leukemia and fou out of fi e acute cases belong to the myeloid type.[illegible] Acute leukemia[illegible] usually starts with enlarged tonsils stomatitis and/or upper respira tory infection of more than usual persistence and severity Hemorrhages from mucous membranes particularly of the nose and gums are an early symptom which persists throughout the disease Anemia develops rapidly Splenic

[illegible] Kandel E V Chloroma Arch Int Med [illegible]
[illegible] Gerrison M Ram lek A A and Rubinstein R I Congenital Leukemia With "Chloroma, Am J Dis Child [illegible] 1930
[illegible] Forkner C E Acute Especially Monocytic Leukemia Arch I Med [illegible] 1934

enlargement often causes abdominal tenderness. Due to the increasing hemorrhagic diathesis bronchopneumonia or sepsis death ensues within four weeks or less in 60 per cent of the patients and within eight weeks in 84 per cent.[illegible] None of 113 cases lived longer than twenty-six weeks.

The white cells, which dominate the blood picture with usually over eighty per cent are uniform and immature mostly myeloblasts less often lymphoblasts or monoblasts. The blood platelets run low and the coagulation and bleeding times are prolonged. The absolute number of leukocytes may be about normal. Leukopenia is common in the early stages.

Skin and Mucosal Manifestation. — Forkner[illegible] emphasizes the importance of initial gingivitis as an aid in differentiation of the acute leukemias. It is most marked and diffuse in monocytic leukemia. Here it may extend to the pharynx usually causing ulceration and bleeding. More than in the other types, a diffuse cellulitis is apt to appear about the lesions causing tooth ache and painful acute inflammation in the deeper tissues of the face. The patients are usually first seen by a dentist. If teeth are extracted the bleeding is severe and sometimes fatal. Deep necroses have followed such extractions. Several authors emphasize the "submerging" of the teeth in the swollen pale pink soft and tender gums which bleed easily.[illegible] The oral aspect sometimes resembles scurvy. Besides the gingivitis gangrenous punched-out ulcerations in the floor of the mouth occur. The necrotic character of the leukemic infiltration may dominate the changes in the tonsils and the lymphoid tissues of Waldeyer's ring.[illegible] Noma resembling pictures may ensue.[illegible]

The nonspecific as well as the specific skin manifestations in acute leukemia are essentially the same as in the chronic cases. However the nonspecific eruptions seem to have a purpuric tendency and the specific leukemic lesions show a greater tendency to regressive changes like central softening ulceration necrosis and gangrene. This is illustrated by the observations of severe necroses after minor operations performed on acutely leukemic patients. The deep and wide necrosis after the application of a vesicant (Leube and Fleischer after Arzt and Fuhs[illegible]) belongs here too. The morphology follows the familiar patterns of papular rashes[illegible] nodules tumors, plaques and erythroderma.[illegible]

[illegible] Warren, S. L. Acute Leukemia, Am. J. M. Sc. 178: 490-500 1929.

[illegible] FitzGerald, L. M. Oral Lesions in Leukemias. J. Am. M. Soc. 33: 471-478, 1942.

[illegible] Pasternack, J. G., Abbot, O. A. and Werner, H. D. Leukemic Gingivopathy. Case of Acute Aleukemic Leukemia. J. Am. Dent. A. 29: 1193-1197 1942.

[illegible] Osgood, E. E. Monocytic Leukemia. Report of 6 Cases and Review of 127 Cases. Arch. Int. Med. 109: 431-451 1937.

[illegible] Hern, A. Klinische Beobachtungen bei der Lymphogranulomatose. Wien. Arch. f. inn. Med. 24: 437-454 1934.

[illegible] Karl, W. Acute Myeloblasten-Leukämie. Zbl. 84: 73.

[illegible] Cohen, I. Cutaneous Tumors in Acute Myeloid Leukemia. Nederl. tijdschr. geneesk. pp. 1061-1053 1936. Zbl. 84: 172.

[illegible] Epstein, T. Fall von akuter aleukämischer lymphatischer Leukämie mit ausgebreiteter spezifischer Hautveränderung. Festschr. f. [illegible] pp. 43-49, 1928. Zbl. 29: 462, 1929.

[illegible] Saidberg, F. Zur Klinik der Leukaemia cutis. Venerol. 7: 33-37 1930. Zbl. [illegible] 1931.

[illegible] Zimmermann, O. Zur Kasuistik der Erythrodermie mit Uebergang in Leukämie. Klin. Wchnschr. 13: 906-909, 1934.

The histology of leukemic lesions of the skin and mucous membranes is of marked uniformity. There is a more or less dense infiltration of the superficial or deep layers of the cutis, composed of the characteristic leucocytes. The infiltrates often form perivascular sheaths, but in fully developed lesions the accumulation of cells throughout the dermis is so dense that the perivascular arrangement disappears.

Hodgkin's Disease

Lymphogranulomatosis (Paltauf and Sternberg)

Hodgkin's disease is a chronic disorder of the lymphatic system. It starts in sixty five per cent of the cases with the painless enlargement of cervical lymph nodes. Gradually other groups and finally the entire lymphatic system including the spleen and often the liver become involved. The enlarged lymph nodes may become large tumors which cause severe local symptoms, especially in the mediastinum. Chronic intermittent fever, weakness, loss of weight, cough, edema, diarrhea, anemia and finally cachexia are the usual features. The blood picture is not characteristic but anemia is common. Eosinophilia is present in 20 per cent and leucocytosis is an occasional finding. The course may be rapidly fatal or slowly progressive over one to rarely more than three years. A few instances of survival for much more than ten years are known.

The disease is most common in the third decade of life but no age or race is immune. Three out of five cases are in men.

Dermadromes.—The incidence of skin manifestations in lymphogranulomatosis follows, generally, the pattern of the other lymphoblastomas. There are nonspecific and specific dermadromes. The former are common and the latter are rare.

Nonspecific Cutaneous Manifestations.—The large series vary in their observations on *pruritus* in Hodgkin's disease. Thirty two per cent (Burnams after Baum[illegible]), eighteen per cent,[illegible] six per cent[illegible] and three per cent (Longcope after Baum[illegible]) are some of the percentages. Especially in France pruritus seems to be considered so common that lack of it prompted publication of three cases.[illegible] Pruritus is often an early symptom which may precede the lymphadenopathy by as long as two years.[illegible] High blood sugar or unexpected high urine sugar

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[illegible] Baum, F. Atypical Cutaneous Symptoms in Lymphogranulomatosis, Arch. f. Dermat. u. Syph. 176: 418–434, 1938.

[illegible] Berger, R. K., and Lehman, E. P. 84 Cases of Hodgkin's Disease, Arch. Surg. 43: 630–649, 1941.

[illegible] Oakey, R. S. J. Hodgkin's Disease, 52 Cases, Hahnemann Monthly 79: 139–149, 1944.

[illegible] Polano, R., Zaccoli, G. and Recordier, M. Trois nouveaux cas de lymphogranulomatose maligne sans prurit et sans éosinophilie, Sang 3: 530–534, 1929.

[illegible] Ambler, J. V. Hodgkin's Disease, Arch. Dermat. & Syph. 25: 1140–1150, 1932.

[illegible] Madden, J. F. Gangrenous Herpes Zoster in Hodgkin's Disease, Arch. Dermat. & Syph. 39: 715, 1939.

enlargement often causes abdominal tenderness. Due to the increasing hemorrhagic diathesis, bronchopneumonia or sepsis, death ensues within four weeks or less in 60 per cent of the patients and within eight weeks in 84 per cent.[illegible] None of 113 cases lived longer than twenty-six weeks.

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[illegible] Warren, S. L.: Acute Leukemia, Am. J. M. Sc. 178: 490-500, 1929.

[illegible] FitzGerald, L. M.: Oral Lesions in Leukemias, J. Iowa M. Soc. 33: 424-426, 1943.

[illegible] Pasternack, J. G., Abbott, G. A. and Werner, B. D.: Leukemic Gingivitis by Case of Acute Aleukemic Leukemia, J. Am. Dent. A. 29: 1193-1197, 1942.

[illegible] Osgood, E. E.: Monocytic Leukemia. Report of 6 Cases and Review of 127 Cases, Arch. Int. Med. 59: 931-951, 1937.

[illegible] Herz, A.: Klinische Beobachtungen bei der Lymphogranulomatose, Wien. Arch. f. inn. Med. 24: 437-451, 1934.

[illegible] Kerl, W.: Akute Myeloblasten-Leukämie, Zbl. 54: 72.

[illegible] Osben, I.: Cutaneous Tumors in Acute Myeloid Leukemia, Nederl. tijdschr. v. geneesk. pp. 1061-1033, 1930. Zbl. 64: 172.

[illegible] Epstein, T.: Fall von akuter aleukämischer lymphatischer Leukämie mit ausgebreiteter spezifischer Hautveränderung, Fortschr. f. Behn. Ents. pp. 43-49, 1929. Zbl. 29: 603, 1929.

[illegible] Saldberg, F.: Zur Klinik der Leukaemia cutis, Venerol. 7: 33-37, 1930. Zbl. 36: 309, 1931.

[illegible] Zimmermann, O.: Zur Kasuistik der Erythrämie mit Uebergang in Leukämie, Klin. Wchnschr. 13: 666-669, 1934.

especially in children[illegible] Desquamation and dryness[illegible] without other characteristics of erythroderma, as well as petechiae are often noticed. Herpes zoster well known as a dermadrome in other lymphoblastomas occurs in lymphogranulomatosis, too[illegible]



Fig 315—Hodgkin disease Nonspecific violently itching eruption Note deep scratches Subsided after x-ray treatment of mediastinal and inguinal lymphatic nodes

Generalized exfoliative erythroderma may be nonspecific or specific, or at first the former then the latter It occurs in all degrees of severity Its clinical

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[illegible] Feer W Lymphogranulom bei Kindern, Jahrb f Kinderh 123 145-160 [illegible]

[illegible] Scherenhof, [illegible] Die Lymphogranulomatose der Haut Handb d H [illegible] Gk 8, 1 271-[illegible], 1939

[illegible] Tube F Lymphogranulomatose mit eigentümlichen Verhornungsstörungen der Haut, [illegible] [illegible] 11 1910-1211 1929 Zbl [illegible] 791

[illegible] Ronchese F Ichthyosiform Atrophy of Skin in Hodgkin Disease Arch Derm & Syph. 47 778-781, 1943.

[illegible] Pendergrass, E and Pancoast, H K Herpes Zoster in Hodgkin Disease Am J M Sc 168 326-333 192[illegible]

picture hardly differs from that in lymphoid leukemia.[illegible] Ichthyosiform keratosis has been observed.[illegible]

Edema is a feature in advanced Hodgkin's disease. It may involve a vast area or the whole body and be part of the cachexia. Of greater dermatological interest is the localized elephantiastic edema of the penis and scrotum[illegible] and of the hands and feet.[illegible] Melanoderma may reach degrees which suggest Addison's disease. Such pigmentations have been observed in cases without preceding x ray or arsenic medication.[illegible] Hodgkin's disease has several times been seen to develop following unusually heavy pigmentation from sunlight exposure.[illegible]

Specific Dermadromes.—*Tumors and Ulcerations*.—This group includes papular rashes as well as infiltrations and larger lesions which one would be more inclined to call tumors. They are all of the same nature. There is no need to form a separate group of lymphogranulomatous ulcerations of the skin since no ulceration occurs without a preceding tumor.

Papular rashes consisting of more or less densely[illegible] placed cutaneous papules, resemble in their clinical appearance those encountered in leukemia. *They may develop from preceding prurigo lymphatica.*[illegible] *A difference may* perhaps be seen in the more pronounced regressive tendency of the lesions. Erosion, ulceration and healing with scarification or central depression is common.[illegible] The lesions may be situated in varying depths of the cutis and subcutis, thus varying in color and palpability. The rash mostly covers the trunk with a certain predilection for the sternal area. In some cases the lesions are grouped together in circinate[illegible] or corymbiform arrangement (Brunsgaard after Schoenhof[illegible]). The number of such observations, however, is too

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[illegible] Schreiber. Lymphogranulomatose. Zbl. 40: 807, 1932.

[illegible] Loveman, A. B. Cutaneous Manifestations of the Lymphoblastomas, Hodgkin's Disease. J.A.M.A. 104: 1892-1896, 1935.

[illegible] Whitley, J. E. M. Hodgkin's Disease With Erythrodermia, Proc. Roy. Soc. Med. 31: 81, 1938.

[illegible] Brack, C. Lymphogranuloma cutis maligna mit eigenartigen Hautveränderungen. Acta dermat. 20: 893, 1930.

[illegible] Löbe. Universelle Erythrodermie bei Hodgkinscher Krankheit. Zbl. 42: 603.

[illegible] Gougerot, H., Blum, P., Oberling and Eliascheff, O. Atrophie de l'épiderme et du derme superficiel et desquamation intense généralisée de la peau (pseudo érythrodermie) dues à une lymphogranulomatose typique. Arch. dermat.-syph. Hôp. St. Louis 4: 319-360, 1932.

[illegible] Tommasi, L. Pityriasis rubra di Hebra-Jadassohn in soggetto affetto da linfogranulomatosi maligna di Sternberg-Paltauf. Gior. ital. di dermat. e sif. 71: 1240-1245, 1930.

[illegible] Spiera, G. Di un caso di linfogranuloma Paltauf-Sternberg (Eritrodermia pitiriasica tipo Hebra). Policlinico (sez. med.) 36: 358-403, 1929.

[illegible] Toppener. Lymphogranulomatosis (Paltauf-Sternberg) of Skin, Arch. f. Dermat. u. Syph. 181: 720-760, 1941.

[illegible] Sanchez-Covisa, J. and de la Cuesta, L. Elephantiasis of Penis and Scrotum in the Course of Malignant Lymphogranulomatosis (Paltauf-Sternberg). Actas dermo-sif. 22: 734-738, 1930.

[illegible] Farkas, O. Lymphogranulomatosis, Zbl. 44: 361, 1933-1933.

Riehl, G., Jr. Pigmentierung bei Lymphogranulomatose (Paltauf-Sternberg). Zbl. 56: 5, 1937.

[illegible] Graham-Little, E. Lymphogranuloma cutis, Proc. Roy. Soc. Med. 23: 1480, 1932.

[illegible] Sweitzer, S. E. and Wiser, L. H. Ulcerative Hodgkin's Disease. Arch. Dermat. & Syph. 21: 220-226, 1930.

[illegible] Nobl, G. J. veslle tuberöse Lymphogranulomatose, Wien. klin. Wchnschr. 46: 717-719, 1933.

[illegible] Bernick, S. R. Cutaneous Hodgkin's Disease With Terminal Blood Stream Spread, J.A.M.A. 126: 1035-1036, 1944.

[illegible] Read. Lymphogranulomatosis cutis, Zbl. 56: 807, 1937.

[illegible] Dittrich. Lymphogranulomatose der Haut, Zbl. 41: 606.

[illegible] Waugh. Hodgkin's Disease. Arch. Dermat. & Syph. 21: 124, 1930.



Fig 316



Fig 317



Fig. 318.

Fig 316 — Papulo-nodular specific eruption in Hodgkin's disease

Fig 317 — Papulo-nodular specific eruption in Hodgkin's disease

Fig 318 — Hodgkin's disease. Papulo-nodular specific eruption and transition to exfoliative erythroderma.
(From Barth [illegible] J. A. M. A.)

small to draw conclusions with regard to an infectious nature The grouped lesions link with the cases with large tumors in small numbers A large node or plaque may be surrounded by satellites.[illegible] Such plaques may reach hand size or may cover half of the scalp or even half of the chest[illegible] or one groin[illegible] These giant plaques are quite suggestive of Hodgkin s disease and are rarely found in other lymphoblastomas Tumors of the face[illegible] and of the ear lobes[illegible] sometimes in symmetrical arrangement [illegible] may create a facies leonina Local trauma may be followed by development of tumors. The consistency of the tumors



Fig 319 Hodgkin disease Ulcerated cutaneous tumor of the anterior chest wall

varies with the depth and the degree of regression and scarring An uneven firmness is a frequent finding (Wirz after Schoenhof[illegible]) The color of these lesions is described as red to dirty yellowish and brown Most describers emphasize the tendency to ulceration and sinus formation[illegible] The whole giant tumor plaque may become an ulcer with undermined[illegible] or infiltrated edges leading to invasion of deeper structures even bones.

[illegible] Greenhouse C A and Cornell, V H Lymphoblastoma (Hodgkin Disease) of the Scalp. Case, Arch Dermat & Syph 29: 560-573 1934

[illegible] Kierland R R and Montgomery H Cutaneous Ulcerative Hodgkin's Disease Proc Staff Meet Mayo Clin 16 124 125, 1941

[illegible] Brain, R J Hodgkin Disease With Dermal and Subdermal Nodules and Purpura, Brit J Dermat 42: 443-448, 1930

[illegible] Rulison, R H Hodgkin Disease of the Lymphatic System and of the Skin, Arch Dermat. & Syph. 36 1203-1208 1937

Sometimes underlying structures like lymphatic nodes are primarily in volved, and the skin is invaded later in a scrofuloderma-like fashion [illegible]

Specific oral lesions seem to be rare [illegible] Paltauf[illegible] suggested that the lym phatic tissues of Waldeyer's ring were the portal of infection but clinical oral or pharyngeal symptoms are very rare considering the frequency of cervical lym phomas. Only a few cases of ulcerative tonsillitis followed by specific neck nodes have become known [illegible] The rarity of tonsillar lesions compared with the frequency of cervical lymph node involvement does not rule out the tonsils as portals of entry [illegible]

Infiltrations and aphthoid lesions of the tongue as well as buccal pigmenta tions,[illegible] have been seen In one case the tongue and oral mucosa and the glans penis showed a patchy exfoliation without any other skin manifestations.[illegible]

Diagnosis and Histology —The diagnosis of cutaneous lymphogranulomatosis rests mainly on the diagnosis of systemic Hodgkin s disease and on the histological findings in lymph nodes and in the skin lesions. The use of stained lymph node imprints on glass slides for the demonstration of characteristic cells has lately been recommended.[illegible] The specific lesions consist of foci of dense cellular in filtration in the corium and in the subcutaneous tissues. The infiltrate is made up of lymphoblasts small lymphocytes plasma cells, fibroblasts epithelioids mast-cells and granulocytes. Among the latter eosinophiles are sometimes found in large numbers The most characteristic cell of the polymorphous granulation tissue is a large cell with much protoplasm and containing one or several deep-staining nuclei. These nuclei are usually large and rich in chromatin and contain nucleoli which sta n deeply with eosin Less often the nuclei are pale (Sternberg after Schoenhof[illegible]) These are the so-called Sternberg and Dorothy Reed giant cells. They are irregularly scattered throughout the granulation tissue which uggests a process of chronic inflammation rather than neoplasm However transformation into true sarcoma occurs.

Tappeiner[illegible] emphasizes the almost constant occurrence of lipid filled phagocytes (pseudoxanthoma cells)

[illegible] Pick, W Lymphogranulom, Ibid 40 14

[illegible] Étienne O Drouet, P L Florentin, P and Louyot, P Observation d' cas de forme cutanée ulcéreuse de la lymphogranulomatose maligne, Bull et mém Soc Méd d hôp de Paris [illegible] 1144-1148, 193[illegible].

[illegible] Senear F E and Caro M R. Ulcerative Hodgkin Disease of the Skin, Arch. Dermat & Syph [illegible] 14- [illegible] 937

[illegible] Paltauf R Ueber die Eintrittspfort des Virus der Lymphogranulomatose Wien klin. Wchnschr 42: 437-[illegible] 1929

[illegible] Nicolas, J Massia, G and Rousset J Un cas d adénie éosinophilique prurigène (maladie de Paltauf-Sternberg Bull Soc franç de dermat et syph [illegible] [illegible]-372, 193[illegible]

[illegible] Zehlin S Eine seltene Rachenveränderung bei Lymphogranulomatose Monatschr f Ohrenh. 63 778-783, 1929

[illegible] Bacher F Lymphogranulomatose mit Hauterscheinungen, Arch f Dermat. Syph [illegible] 21-30 1931

[illegible] Tharlit H Hodgkin Disease Surface Lymphogranulomatosis Confined t he Oral and Penile Mucosa Case Arch Derma & Syph 24 [illegible]-290, 1931

small to draw conclusions with regard to an infectious nature. The grouped lesions link with the cases with large tumors in small numbers. A large node or plaque may be surrounded by satellites.[illegible] Such plaques may reach hand size or may cover half of the scalp or even half of the chest[21] or one groin.[illegible] These giant plaques are quite suggestive of Hodgkin's disease and are rarely found in other lymphoblastomas. Tumors of the face[illegible] and of the ear lobes,[illegible] sometimes in symmetrical arrangement,[illegible] may create a facies leonina. Local trauma may be followed by development of tumors. The consistency of the tumors



Fig. 219.—Hodgkin's disease. Ulcerated cutaneous tumor of the anterior chest wall.

varies with the depth and the degree of regression and scarring. An uneven firmness is a frequent finding (Wirz after Schoenhof[illegible]). The color of these lesions is described as red to dirty yellowish and brown. Most describers emphasize the tendency to ulceration and sinus formation.[20] The whole giant tumor plaque may become an ulcer with undermined[illegible] or infiltrated edges, leading to invasion of deeper structures, even bones.

[illegible] Greenhouse, C. A., and Cornell, N. H.: Lymphoblastoma (Hodgkin's Disease) of the Scalp. Case, Arch. Dermat. & Syph. 29: 566-573, 1934.

[illegible] Kierland, R. R., and Montgomery, H.: Cutaneous Ulcerative Hodgkin's Disease, Proc. Staff Meet. Mayo Clin. 16: 124-128, 1941.

[illegible] Brain, R. J.: Hodgkin's Disease With Dermal and Subdermal Nodules and Purpura, Brit. J. Dermat. 42: 445-448, 1930.

[illegible] Rulison, R. H.: Hodgkin's Disease of the Lymphatic System and of the Skin, Arch. Dermat. & Syph. 36: 1202-1203, 1937.

nodules in the skin or in the subcutaneous tissue. Their number may be very great [2941,2946-2948] There is a definite tendency to spontaneous regression which is rarely found in metastases of other malignant tumors. The metastatic nodules are occasionally seen in close proximity to the primarily involved lymph node.[2941]

Sometimes mediastinal lymphosarcoma penetrates the chest wall and invades the skin Even such advanced lymphosarcoma may still be clinically curbed by x ray therapy The incidence of metastatic nodules in the skin is given as 5 per cent[2947] and as 13 9 per cent of 122 cases.[2949]

The diagnosis is usually assured by biopsy There is profuse proliferation of a single type of cell invasion of the capsule of the node and the neighboring tissues, abundance of atypical lymphoid cells without notable endothelial and reticulum hyperplasia and lack of Sternberg Reed cells.[2949] Differentiation from other lymphoblastomas is not always possible.[2949] The therapy is radiological and surgical

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[2946] Riehl, G Jr Hautveränderungen bei aleukämischer in Lymphosarkomatose übergehender Lymphadenose, Arch. f Dermat. & Syph. 169: 800-811 1933

[2947] Riebes Fall zur Diagnose, Zbl. 45: 11

[2948] Flesch Lymphosarcomatosis Cutis, Zbl. 39: 619.

[2949] Cohn, R., and Richter M Modern Views on Hodgkin's Disease M Rec. 148 343 1938.

CHAPTER XXXIII

DISORDERS OF THE BLOOD AND THE BLOOD FORMING ORGANS

Anemias[illegible]

The red blood cells are formed from endothelium in the red bone marrow. They pass through various stages of development (megaloblast, normoblast, reticulocyte) before they are released into the blood stream. Besides the material necessary for the development of all cells, two specific substances are required for the normal development of erythrocytes: iron for the formation of hemoglobin and the erythrocyte maturing factor (EMF) which is produced in the gastric mucosa and stored mainly in the liver. After a life span of from two to six weeks, the red cells die and their remnants are phagocytized by the reticulo-endothelial cells in the spleen. Eighty-five per cent of the iron is used again, and bilirubin, the other end product, is under normal conditions excreted by the liver.

The function of the red cells is the transport of oxygen from the lungs to the tissues. Anemia is a reduction below normal of the capacity of the blood to transport oxygen.[illegible] It may result from too small numbers of functioning red cells or from deficiency in their function, due especially to lack of hemoglobin. The clinical forms and stages of anemia are mostly explained by the phase in which a damaging influence hits the growing or mature red cell. For example, in the case of anemia from massive hemorrhage the mature cells are reduced in number. In the case of pernicious anemia the maturing of the red cells within the bone marrow is disturbed by a deficiency of the E.M.F. and so they die to a large extent in the bone marrow, only an insufficient number of immature cells being released. The bilirubin left over from the hemoglobin of the masses of dead red cells increases the bile pigment in the blood and may cause icterus.

Dermadromes.—*Pallor* is seen in practically all anemias and is directly proportional to the loss of hemoglobin.[illegible]

In *hypochromic anemia* (chlorosis), which is rare today, the pallor sometimes takes on a slightly greenish tinge. Capillaroscopy shows the capillaries in various types of severe anemia to be pale, thin, or even empty and filament like with the arterial and venous sections hardly discernible.

The estimation of pallor from the face and the mucosae is often deceiving. Duke advises a quick test: compare the palms of the patient with those of a normal person. The palms should be held at heart level. The advantage of the test, which supposedly is quite accurate, is the independence of the palms to emotional erythema and light.

[illegible] Meulengracht, E.: Some Etiological Factors in Pernicious Anemia. A Symposium on the Blood and Blood Forming Organs, Madison, Wis., 1939, the University of Wisconsin Press.

Chevallier[1441] enumerates the following dermatoses as occasionally seen in essential anemias Rhagades of the fingertips and lips smooth atrophic tongue and buccal mucosa pruritus vulvae precocious graying of the hair and intertriginous erythema. Corroboration of these impressions is still lacking although a similar list which includes collonychia is given by Simon[1442]

Pernicious Anemia

Besides the pallor found in other anemias too a yellowish *discoloration* is characteristic of this disease It is caused by the increased content of bilirubin from prematurely destroyed red cells and to a lesser extent from other substances in the blood plasma The icteric index may be above ten normal is four to six. The third factor which influences the color in pernicious anemia is pigmentation which though rarely may reach degrees which suggest Addison s disease. The pigmentation is mostly described as diffuse sometimes it has a predilection for the trunk, chest abdomen and the dorsa of the hands. As in Addison s disease the creases folds or scars may be darker than the surrounding skin[1443] Freckled or lentigo-like spots have been seen within the diffuse melanoderma (Lennartz after Kaufmann[1286]) Another similarity to Addison s disease is found in slate-colored or brownish spots on the oral mucosa. Not only may the symptoms of Addison s disease occur in pernicious anemia but even post mortem findings of adrenal atrophy are on record.[1339] Bogorad[1443] saw improvement of the pigmentation under cortin while liver therapy alone failed to change it. Most authors suggest that the melanosis in pernicious anemia is a hemosiderosis derived from the blood but the histological evidence is scanty and not clear[1441-1446] The possibility of arsenical melanosis must be considered since arsenic was and still is used in pernicious anemia Patients with pernicious anemia under treatment with liver extract are supposed to tan more readily than normal persons.[1446] In a very extensive case of cutaneous and mucosal pigmentation in pernicious anemia the author could not notice any effect of liver therapy on the pigmentation despite good response of all other symptoms. Ulcers of the lower legs which are more often seen in other forms of severe anemia are very rare in pernicious anemia[1447]

The symptom known as *Möller s or Hunter s glossitis* is of practical importance because it may precede all other complaints and the hematological findings

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[1441] Chevallier P Die Dermatosen der Anaemie, Med. Welt 10: 120-122, 1936.

[1442] Simon, C. Anémie, etc., Paris méd. 1 47-51 1936.

[1443] Bogorad, A. G Hyperpigmentation of Skin in Biermer' Anemia, Klin. med 18: 94-96, 1940-Ref. 29: 104.

[1444] Sequeira, J H and Panton, P N Case of Erythrodermia With Lymphocytosis, Brit. J Dermat. 33 373 1921

[1445] Gansleber E. Hautpigmentation und Hautreaktion bei perniziöser Anämie Deutsche med. Wchnschr 57: 1074 1931

[1446] Tscherney T Pigmentierungen der Haut bei perniziöser Anämie, Arch. f. Dermat. u. Syph. 121 746-761, 1916.

[1447] Lasch, F Beingeschwüre bei perniziöser Anämie Deutsche med. Wchnschr 62 377-378 1936

PLATE V

1 Pellagra. Erythema of dorsum manus. (Courtesy Wisconsin General Hospital.)

2 Scurvy. Gingivitis. (Courtesy Wisconsin General Hospital.)

3 Ecchymoses in acute lymphatic leukemia. (Patient of Dr. F. Kay.)

4 Pernicious anemia, untreated. Acute glossitis involving mainly the edges. Filiform papillae are still present. Note ecchymosis.

5 Pernicious anemia. Pale slick tongue. Atrophy of papillae.

6 Erythema nodosum.








PLATE V

in pernicious anemia.[illegible] The condition starts with a burning sensation in the tongue and occasionally in other parts of the mouth The pain and sensitivity to acid hard food and smoking often comes in spells. Sometimes articulation is hampered In some cases only burning is noticed and no visible changes develop but more often fiery red painful round or oblong erosions appear usually on the dorsum close to the tip The filiform papillae within the patches are at first swollen but soon thinned or absent the fungiform papillae are often swollen and red.[illegible] The tip and the edges occasionally also the adjacent parts of the dorsum of the tongue are involved but sometimes also the inside of the lips,



A B

Fig. 220.—A Pernicious anemia Subchronic changes The papillae filiformes have mostly disappeared B. Pernicious anemia Atrophy of papillae.

cheeks and the palate (Harris after O H Foerster[illegible]) From the distribution on the tongue a "V" or "U" shaped figure results with the opening directed toward the base of the tongue Many authors[illegible] emphasize the contrast of the fiery red lesions on the tongue to the pallor of the other parts of the oral mucosa while others say that the red areas are the healthy ones and the pale areas the changed ones.[illegible] These may represent later stages of development. The initial erosion is later followed by atrophy of the papillae which results in a smooth surface In extreme cases the atrophy may involve the posterior part of the tongue and the

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[illegible] Mager W Zur Kasuistik der Glossitis bei perniciöser Anämie Monatschr f Ohrenh 66 318-21 1932.

[illegible] Heyn, W Möller'sche Glossitis, Hunter'sche Zunge und perniciöse Anämie Dermat. Ztschr 47 133, 1926

[illegible] Hasselkuss, A Moeller'sche Glossitis, Diss Berlin, 1931 Zbl 39 782.

[illegible] Hunter W Severest Anaemias Their Infective Nature Diagnosis and Treatment, London, 1909.

[illegible] Foerster O H Dermatoses and Associated Diseases of the Mucosae J.A M A 73: 653 1919

[illegible] Zlosser E Hautkrankheiten und Mundkrankheiten Möller'sche (Hunter'sche) Glossitis, Handb. d. H Ok, 14, 1 11 1930.

papillae vallatae Slight edema of the tongue with visible impressions o he teeth has often been noticed in the early stages (Hunter's[3061] hacked edges')

Though most frequently seen in pernicious anemia Möller Hunter's glossitis or similar conditions occur in other severe anemias (tropical and nontropical sprue pellagra alcoholism tapeworm etc.)[3064] The painful red erosions of Möller Hunter's glossitis should not be confused with the dry round sharply outlined plaques fauchées which are seen in syphilis or with the harmless plaques lisses which consist of non inflammatory round areas which are devoid of papillae These completely painless lesions are usually accidental findings. The transitory character and the fast traveling over the dorsum within a few days are characteristic of the wandering rash of the tongue The restriction of a chronic inflammation to a diamond shaped area in the center of the posterior tongue marks the rhombic median glossitis.[3065] Liver therapy relieves the glossitis in pernicious anemia and so it has become rather rare If the patient sticks his tongue out anemic stripes appear which correspond to the contracted muscles (Arndt after Heyn[3049]) This sign is considered valuable in early diagnosis. The tongue is hardly ever coated

Sickle Cell Anemia

This is a severe hereditary anemia which derives its name from the characteristic sickle- or spindle-shaped erythrocytes (drepanocytes) which occur in great numbers as do other bizarre forms of the red cells. The disease has almost exclusively been seen in Negroes in a few instances in Sicilians.[3066] Jaundice is almost always noticeable[3067]

Dermadromes.—Punched out sometimes serpiginous unilateral or bilateral extremely chronic ulcers near the ankles are common in this anemia They were seen in twenty out of twenty-eight cases[3067] and in 55 out of 214 cases.[3068] These ulcers often develop after minor injuries. Poor circulation in the lower legs and the known tendency to thrombosis in sickle cell anemia probably are pathogenetic factors Priapism which has repeatedly been seen in sickle cell anemia also can be explained by thrombosis in the vascular system of the penis.[3069]

Therapy of the ulcers should consist of nonirritating local medication and treatment of the underlying anemia.

Similar leg ulcers have been seen in a considerable number of cases of *hemolytic anemia* (hemolytic jaundice) This is a hereditary anemia characterized by unusual spheroid shape of the erythrocytes. These ulcers sometimes only heal

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[3064] Manson Bahr P H Glossitis and Vitamin B Complex I Pellagra, Sprue and Allied States, Lancet 2: 317 356, 1940

[3065] Brocq and Pautrier Glossite losangique médiane Ann de dermat et syph 5: 1 1914-1915

[3066] Greenwald, L and Burrett J B Sickle-cell Anemia in White Family Am J M. Sc 199 768-774, 1940

[3067] McGavack, T H and Nussbaum, C C Skin Manifestations of Sickle Cell-Anemia, Urol. & Cutan Rev 46 194-200 1942

[3068] Cummer C L and LaRocco C G Ulcers of Legs in Sickle Cell Anemia, Arch. Dermat & Syph 42: 1015-1039 1940

[3069] Getzoff P L. Priapism and Sickle Cell Anemia J Cases J Urol, 48 07-411 1942.

after splenectomy [illegible] The jaundice in hemolytic anemia supposedly does not itch as other types of icterus usually do [illegible]

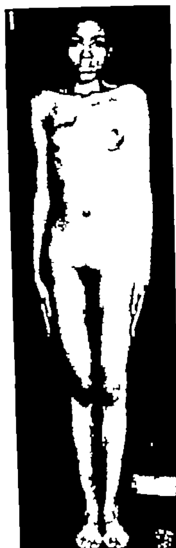


Fig 331 – Female aged 18 years Sickle cell anemia Leg ulcer (From McG vack, T H, Urol. & Cutan. Rev 1942)

[illegible] Taylor E. S Chronic Ulcer of the Leg Associated With Congenital Hemolytic Jaundice J A M A 1[illegible]: 1574 1930

[illegible] Estape F de A Ulcus cruris y esplenectomia en ictericia hemolítica, Rev de cir Barcelona [illegible] 47-[illegible], [illegible]31

[illegible] Lanz, F J Unterschenkelgeschwür bei hämolytischem Ikterus Klin Wchnschr 10 409-410 1931

[illegible] Eppinger H Schwer heilbare Fussgeschwüre bei hämolytischem Ikterus, Klin W hnschr 9 10-12, [illegible]30

[illegible] Peppe E Ein Fall von icterus haemolyticus mit Unterschenkelgeschw. [illegible] Milzexstirpation, Norsk mag f laegevidensk 96 703-710, 1934 Zbl [illegible] 225.

Hypochromic Anemia Plummer Vinson Syndrome —Dysphagia, an atrophic oral mucosa anemia and often spoon nails or thin nails constitute a syndrome which does not seem to be rare Described by Vinson[3475] in 1922 as hysteric dysphagia but observed before it has been confirmed by reports from many countries It seems to occur more frequently in Sweden than in other countries.[3476] The patients are almost exclusively women mostly in middle age. Idiopathic hypochromic anemia with pallor but without jaundice is the most



Fig [illegible] —Female aged 16 years Severe sickle cell anemia Hemoglobin 40 per cent R B C 1.66 million. Hemolytic icterus Amenorrhea Ulcer of the lower leg exists for [illegible] years without any response to treatment I developed after dog bit (From McG [illegible], T H Urol & Cutan Rev 1943)

constant feature of the syndrome [3477] The red cells usually do not fall below 4 000 000 but the hemoglobin is reduced to 50 per cent or less. Achlorhydria is seen in 75 to 90 per cent of the cases and moderate splenomegaly in

[3475]Vinson, P P Hysterical Dysphagia, Minnesota Med 5 107 1922

[3476]Ahlbom, H E Achlorhydric Anemia, Plummer Vinson Syndrome and Carcinoma of the Mouth, Pharynx, Esophagus in Women, Brit M J 2 331-333 1936

[3477]Anderson, N P Spoon Nails, Anemia, Cheilitis and Dysphagia, Arch Dermat & Syph 37 816-833, 1938

25 per cent. Complaints of burning tongue especially after eating fruit and other acid food often lead the attention to the changes in the mucosa of the upper part of the gastrointestinal tract. The patients have great difficulty in swallowing solid food so that their mealtime is prolonged.

They soon arrive at a liquid or semiliquid often deficient diet

Dermadromes and Oral Manifestations.—There is cheilitis varying from minor fissures to hypertrophic chronic inflammation or perlèche. Buccal leukoplakia occurs. After a time the lips become thin and the mouth shrinks. Ahlbom [illegible] who has given a very detailed description believes that the shrinking of the lips is part of the same atrophic process which leads to the changes in the tongue and esophagus. Possibly the fact that these patients often lose their teeth early has some significance The surface of the tongue is described as glazed red dry smooth and devoid of papillae.[illegible]

There is much similarity to Hunter's glossitis but the involvement of the mucosa seems more widespread and more constant. It not only involves the mouth but it extends to the upper—rarely the lower[illegible]—part of the esophagus. Spastic or cicatricial stenosis of the mouth of the esophagus web formation across the lumen ulceration and other symptoms have been seen [illegible] Cancer of the esophagus and multiple oral malignancies have been observed Especially in the relatively rare instances of cancer of the lip in women should the thought of anemia and Plummer Vinson's syndrome enter the mind [illegible] The post-cricoid cancer of the esophagus which in 70 per cent to 90 per cent is encountered in women probably belongs here [illegible] Association of Plummer Vinson syndrome and kraurosis vulvae is also known (Rhoads after P Gross[illegible])

Only recently after many cases of Plummer Vinson's syndrome have been described without mentioning coilonychia have spoon nails been discovered to form a rather frequent (about 70 per cent) dermadrome in hypochromic anemia [illegible] The free edge of the nail is thin and sharp as if gnawed on The nail breaks or splits easily and in less complete cases the nail is only flat and thin It should not be forgotten that coilonychia may be produced by occupational factors, e.g work in soap suds and oils. Dry gray pepper and salt hair are also mentioned in case reports.[illegible] The similarity of Plummer Vinson's syndrome with ariboflavinosis has been emphasized [illegible]

The treatment of the syndrome consists of administration of iron in liquid form hydrochloric acid riboflavin[illegible] and bougieing of the upper esophagus which seems to be particularly helpful in relieving the dysphagia and facilitating a proper diet The oral as well as the nail changes are capable of complete restoration

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[illegible] Kerman J D Plummer Vinson Syndrome 3 Cases, Arch. Otolaryng. [illegible] 1940.

[illegible] Gerlings, P G Disorders of Mouth of Esophagus in Syndrome of Plummer Vinson (Dysphagia With Anemia, J Laryng & Otol [illegible] 143-153, 1940.

[illegible] Dameshek, W Primary Hypochromic Anemia, J.A.M.A [illegible] 1933

[illegible] Meulengracht E and Bichel, J Riboflavin Avitaminosis and Plummer Vinson Syndrome, Klin Wchnschr [illegible] 1941

Granulopenia (Agranulocytosis)

Granulopenia[illegible] is a deficiency of the blood in granulocytes caused by *failure of the bone marrow to produce or release these cells.* It may be caused by toxic and allergic reactions[illegible] to drugs such as arsphenamine trinitrophenol benzol amidopyrine sulfonamides and gold by radiant energy by infection and by allergic reaction[illegible] Granulopenia also occurs secondarily to hyperplastic processes in pernicious anemia or leukemia Low leukocyte count—sometimes as low as fifty—acute sore throat exhaustion severe malaise fever and a moderate degree of icterus are in 50 per cent of the cases the manifestations of this dangerous disease The spleen is often enlarged Cases without any mucosal symptoms occur[illegible] The red cell and platelet counts are essentially unaltered this accounts for the usual lack of hemorrhagic symptoms.[illegible] If they too are deficient (pan myelophthisis) hemorrhages occur[illegible] The resistance to infections is extremely low The mortality in untreated cases was seventy-eight per cent in a large series Death may occur within thirty-six hours from the apparent onset[illegible]



Fig 323 —Agranulocytosis Ecchymosis

[illegible]Hunter R J Agranulocytic Angina, M Clin North America 22 1669-1681 1938.
[illegible]Marin, A La granulopénie maligne Union méd d Canada 69 126, 250 349 400 1940.
[illegible]Madison, F W and Squier T L Agranulocytosis, J.A M.A 102: 755-759 1934.
[illegible]Clemens G Granulocytopenia in Lupus Erythematosus, Dermat. Wchnschr 109 1310-1313 1939
[illegible]Jackson, H J and Tighe T J O Treatment and Mortality of 200 Cases of Acute Agranulocytic Angina, New England J Med 220: 729-733 1939
[illegible]Plum, P Clinical and Experimental Investigations in Agranulocytosis, London 1937 H K. Lewis Co Ltd and Copenhagen, 1937 Nyt Nordisk Forlag Arnold Busck
[illegible]Stasberlin, R Agranulocytose und Panmyelophthise München med. Wchnschr 85 1419-1423 1938.

Oral Manifestation and Dermadromes.—Angina is so much a part of the syndrome that the disease is often referred to as agranulocytic angina Bucco-pharyngeal lesions are seen in 84 per cent [illegible] The soft palate uvula and anterior



Fig 324 —Agranulocytosis. Ecchymoses. (Courtesy Dr Erich Urbach.)

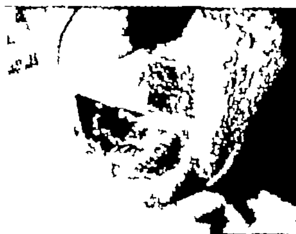


Fig 325 Agranulocytosis Cheilitis and glossitis Patient also had angina.

pillars are red and eroded the redness being sharply bordered against the normal mucosa [illegible] The tonsils are enlarged and red sometimes with small white specks sometimes with severe ulcerations Ulcerations in other part of the oral cavity and also in the nose[illegible] have been observed sometimes without involvement of

[illegible] Retzdi A Granulocytopenia With Peculiar Changes in Nasal Mucosa, Monatschr f Ohrenh. 73 [illegible] 1940

the tonsils.[illegible] Gingivitis with adherent foul smelling pseudomembranes[illegible] is often present The gums bleed easily Rarely the ulcerations invade the bone or spread to the deeper tissues of the pharynx and larynx. Edema of the glottis may necessitate tracheotomy [illegible] Fusiform bacilli and large spirilla are commonly found The cervical lymph nodes are swollen but there is no generalized adenopathy



Fig [illegible] Agranulocytosis due t dinitrophenol poisoning (Courtesy Dr Arthu

The face is often cyanotic sometimes pallid or congested [illegible]

Cutaneous ulcerations about the body openings mainly around the mouth and nose were described by Landsberg [illegible] These necrotic lesions are mostly small [illegible] but severe edema and lymphangitis may be present so that anthrax or other infections are simulated Cellulitis and deep noma-like destructions are rare events. Ulcerations in the neighborhood of the anus[illegible] or the genitalia[illegible] have been observed quite frequently [illegible] Exanthems of erythematous pemphigoid vesicular papular or hemorrhagic[illegible] character and occasionally

[illegible] Bélard, M and Lebourg, L Syndrome agranulocytaire à début buccal Guérison de l ulcération buccale Évolution ers syndrome subictérique vec anémie pernicieuse Rev de st matol. 35 621-627 1933 Zbl 47 584

[illegible] Dahmen Agranulocytose Zbl 48 384

[illegible] Krampe Disc Dahmen, Zbl. 41: 580.

[illegible] Pothoven, W J Bilaterale Larynxnekrose bei Agranulocytose Arch f Ohrenh. 147 196, 1939-1940

[illegible] Helsmoortel, J J and Meulders, M Agranulocytosis With Buccopharyngeal Manifestions 2 Cases, Ann d oto-laryng pp 281-287 1940

[illegible] Landsberg M Hautveränderungen bei Agranulocytose Med Klin 26 1282-1283 1930

[illegible] Buck, R W Agranulocytosis With Anal Ulcer J A.M A 93 1458-1460 1929

[illegible] Reye, E Ueber Haut- und Schleimhautveränderungen bei der Agranulocytose Dermat Wchnschr 89 1898-1900 1929.

[illegible] Fortier L Agranulocytose nécrose cutanée, Union méd d Canada 61 240-250, 1934.

[illegible] Greenbaum, S S Acut Cutaneous Infection Associa ed With Agranulocytosis or Agranulosis, Arch Dermat & Syph 28 125-126, 1933.

[illegible] Dalous and Fabre, J Les lésions cutanées de l agranulocytose Arch d mal d coeur 27 645-656, 1934.

[illegible] Allan, W Agranulocytic Angina With Thrombopenic Purpura, Ann Int. Med. 2 515-544 1928.

typical erythema exsudativum multiforme have been recorded.[illegible] Mann[illegible] has seen giant herpes of the lips. Pentnucleotide in large doses as stimulant for the production of leukocytes is considered helpful by many authors. Otherwise, the therapy is symptomatic. Recently pyridoxin by intravenous injection has been recommended.[illegible]

Polycythemia[illegible]

Compensatory increase of the erythrocytes (above 6 000 000 in men and above 5,500 000 in women) occurs under various *suboxemic conditions* e.g. low barometric pressures, carbon monoxide poisoning and certain types of heart disease. Such secondary increases of the red cells hardly ever exceed 8 000 000. Polycythemia vera is a disease of the bone marrow. In this condition much higher, sometimes enormous, increases of the blood volume and of the red cells per cubic millimeter of blood occur. The viscosity of the highly corpuscular blood, of course, is high. After an asymptomatic phase which may last years cyanosis, dizziness, headache and quite often hepato-splenomegaly develop. Bleeding occurs from the nose and gums due to congestion rather than to a hemorrhagic tendency. Variations of the normal syndrome include combinations of hypertension and especially in the final stages leukemia and anemia.[illegible]

Dermadromes.—The most common and at the same time most striking dermadrome of marked polycythemia is the *redness of the skin*. This discoloration is most marked on the hands and face although in some cases it may be noticed over the entire body surface. The shade and intensity of the erythema varies from a dusky purple cyanosis to a deep or in spots bright red. "Red as a rose in summer and blue as indigo in winter" is descriptive of the changes under the influence of weather and temperature. Osler,[illegible] who used this description, said that one of his patients was jokingly called the "blue baby." There is erythema in areas which usually do not take part in other erythemas, e.g. the temples and the skin under the ears and between eye and nose. The redness of the conjunctivae creates an impression of rage. Contrary to congestion from other causes the redness stays constant during rest and sleep.[illegible] While the erythema seems to be fairly even, one can on close inspection and under glass pressure detect telangiectases on the red background. This is particularly true of the mouth. Capillaroscopy shows that the capillaries are dilated. It is here and in the spleen where much of the excess blood is bottled up.[illegible] Superficial telangiectases of the face often give the patient a ruddy complexion. Besides

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[illegible] Gorter, [illegible]: Agranulocytosis, Nederl. tijdschr. [illegible] geneesk. p. 572, 1939; Zbl. [illegible]

[illegible] Ellison, P. and La[illegible]rence, J.: Agranulocytosis With Purpura Hemorrhagica Following Gold Therapy: Prevention of Complications, Brit. M. J. [illegible] 1933.

[illegible] Kastrup[illegible]: Treatment of Leukopenia and Granulocytopenia With Pyridoxine, Acta Med. Scand. 125: 326, 1946.

[illegible] Rosenthal, N. and Bassen, F. A.: Polycythemia. Course, Arch. Int. Med. [illegible] 903-917, 1938.

[illegible] Osler, W.: Chronic Cyanosis, With Polycythemia and Enlarged Spleen: New Clinical Entity, M. Classics 4: 354-378, 1939.

[illegible] Denecke, G. and Dorkhorn, E.: Polycythemia, Med. Klin. [illegible] 1654-1656, 1930.

[illegible] Brown, G. E. and Sheard, Ch.: Measurements on the Skin Capillaries in Cases of Polycythemia Vera: Rôle of the Capillaries in the Production of Erythrosis, J. Clin. Investigation [illegible] 423, 1926.

linear telangiectases small deep cherry red papular hemangiomas are known to occur in polycythemia

The color of the *oral mucosa* is deep cherry red Relatively early in the course of the disease the soft palate may appear considerably redder than the hard palate so that the borderline is marked [illegible] In the cyanotic stage the tongue is swollen deep purple and the papillae atrophic. Bleeding from the blood gorged gums occurs but is slight since there is no hemorrhagic tendency [illegible]

Small pigmented spots are often scattered over the reddened areas. They are probably due to hemosiderin deposits after small hemorrhages.

Telangiectases and petechiae constitute the elements of *purpura annularis telangiectodes* a dermatosis which has been found to be a dermadrome of a considerable number of milder cases of polycythemia [illegible] Without preceding hyperemia or infiltration small lavender to purplish colored spots appear These maculae consist of capillarectases and petechiae The lesions appear in crops They often start in a follicle and spread peripherally leaving a slightly atrophic scar and resulting in rings[illegible] and polycyclic figures.

The tourniquet test is usually negative

The viscosity of the blood the high platelet content the large blood volume and the high blood pressure favor a variety of *vascular disturbances*

Thrombosis has been observed in many organs and is together with arteritis responsible for gangrene ranging in severity from the blistering of a toe to the loss of an extremity [illegible] Various *ulcerations* of the lower legs have been observed [illegible] Circulatory disturbances account also for the many instances of paresthesias Raynaud-like symptoms and transitory painful red warm areas similar to erythromelalgia[illegible] Norman and Allen [illegible] reporting on ninety eight cases of polycythemia mention arterial disease in 33 per cent.

Rosacea in polycythemia has been described several times, although some of the cases had better be grouped with *acne urticata* a relatively rare dermadrome of polycythemia *Acne urticata* is a chronic itching dermatosis which resembles prurigo quite closely It starts on the face but has a tendency to involve the back and the extensor surfaces It develops from an urticarial papule with a

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[illegible] Kuperman D J Symptomatology of Erythremia, Vest Otol i t d 21 210-218, 1937 Zbl. 57 466

[illegible] Kontejev O Skin Changes and Pathogenesis of Vaquez Disease Venerologia i dermatologia, pp 744-755 1926 Zbl 23 673

[illegible] [illegible] jev [illegible] Changes i Erythremia, Zbl 20 37 1929

[illegible] Get roo H Purpura Majocchii, Arch f Derma Syph 159: 355, 1929

[illegible] Brünauer Purpura annularis telangiectodes Majocchi Zbl 30 587 1931

Weinmann H [illegible] eränderungen bei Polycythemia rubra, Diss Erlangen 1937

[illegible] Becker F Extremitätengangrän bei Polycythaemia vera, Klin Wchnschr 11 1260-1262, 1932

[illegible] Thieme Trophoneurotisches Ulcus, Zbl 25: 706

[illegible] Zeller W J Peripheral Vascular Disturbances i Polycythemia, M Clin North America 24 465-472 1940

[illegible] Hallam Ulcerated Nodules on Legs Associated With Splenomegalic Polycythaemia, Brit J Dermat 42: 282-283 1930

[illegible] Urbach F Ein Fall einer kombinierten Erkrankung von Erythromelalgie und Polycythämie Rosak. Klin 11 28-34, 1929 Zbl. 32 62.

[illegible] Gans, O Polycythemia Vera, Virchow Arch f path Anat 263 365-373 1927 Zbl 21 62.

[illegible] Norman, I. L and Allen, E V Vascular Complications of Polycythemia, Am Heart J 13 257 274 1937

central vesicle which soon becomes excoriated The crust covered lesion may ulcerate and heal with a pigmented scar Crops of new lesions follow each other The condition has much similarity to prurigo lymphatica, which occurs in leukemia. Thus acne urticata represents another link to leukemia which not infrequently constitutes the final stage of polycythemia.[illegible]

The treatment of polycythemia is to remove or destroy the excess of erythrocytes by blood letting irradiation phenylhydrazine arsenic and other drugs.

[illegible] Weidman, F. D., and Klauder J. V. Acne Urticata Polycythaemica Positive Oxydase Reaction in Lesions Macroscopically and Microscopically Arch. Dermat. & Syph. [illegible] 645-666, 1930.

Chapter XXXIV

DISORDERS OF THE BLOOD AND THE BLOOD FORMING ORGANS

Hemorrhagic Diseases

The characteristic common to all diseases of the hemorrhagic group is abnormal bleeding. The flow of blood from an injured vessel starts a sequence of mechanisms. The injured small blood vessel contracts slowing down or stopping the bleeding. Macfarlane[illegible] explains this primary vascular constriction by assuming that the flow of blood removes the dilating histamin like substance released by trauma. Blood platelets then form a clot which is finally reinforced by the formation of fibrin. The vasoconstriction is a quick response which slows the flow of blood sufficiently so that the platelets can collect from the blood and form an adherent thrombus. This clot retracts and closes the wound firmly and permanently. Since the contracted vessels relax after a certain period of time blood would start flowing again and the clot would be pressed out if it had not become firmly adherent and by its power of retraction pulled the walls of the injured vessel together.[illegible] This mechanism of hemostasis may be disturbed in any of its phases. There may be lack of capillary reaction, clotting may fail or a combination of both may occur. Abnormal bleeding will result in any case. Furthermore decreased resistance of the capillary wall is an important factor in many hemorrhagic diseases.

In thrombocytopenic purpura lack of capillary contractility and a low platelet count are combined. The bleeding time is prolonged just as it is in athrombocytopenic purpura where the platelet count is normal. In Osler's disease the trouble is completely vascular and restricted to the capillaries. In hemophilia, fibrinopenia, pseudohemophilia, jaundice and hemorrhagic disease of the newborn defective coagulation is responsible, in the two latter conditions being combined with capillary dysfunction.[illegible]

Capillaroscopic observations[illegible] suggest that the blood of ecchymoses does not come from the capillaries but from the subpapillary venous plexus. Fresh petechiae have a red color. This is probably due to the presence of engorged very superficial small vessels and a small amount of extravasated blood in the upper layers of the cutis. The combination of vasodilatation and free hemorrhage in the deeper layers produces a bluish lesion.[illegible]

Blood Coagulation. The transformation of fibrinogen, a labile colloidal blood protein which is probably formed in the liver or perhaps in the reticulo-

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[illegible] Macfarlane R G: Mechanism of Hemostasis, Quart J Med 10: 1-29, 1941

[illegible] Jürgensen E: Capillarmikroskopische Beobachtungen bei Purpura, Deutsches Arch f klin Med 178: 434-41, 1933, Zbl 47: 479

[illegible] Peck S M, Rosenthal N and Erf L: Purpura: Classification and Treatment With Special Reference to Treatment With Snake Venom, Arch Dermat & Syph 35: 831-867, 1937

endothelial system into fibrin of which the clot mainly consists is only the final phase of the chain of reactions which constitute coagulation The formation of fibrin from fibrinogen needs an enzyme thrombin which is not present in the circulating blood since the blood would otherwise coagulate in the vessels. If needed it is synthesized from a liver protein called prothrombin and free calcium ions. Naturally the prothrombin too must be held inactive under normal conditions. The activator of the prothrombin is thromboplastin which is held ready in the blood platelets.

The most important methods used to diagnose a hemorrhagic disease are [illegible]

1 The *coagulation time* of the blood Normal blood coagulates in a test tube in one to five to eight minutes (Lee and White)

2 The *bleeding time* The skin bleeds from a small cut into the ear lobe for from one to three minutes. The bleeding is recorded by blotting on white blotter every thirty seconds (Duke s method) This demonstrates the capillary reaction to injury

3 The *capillary resistance* This is most readily tested by the *tourniquet test* (Leede-Rumpel test) Haden[illegible] calls the test positive if after placing a blood pressure cuff on the upper arm for three minutes at a pressure of 100 mm of Hg a crop of petechiae appears below and under the cuff According to Quick[illegible] the pressure should be kept for eight minutes midway between the diastolic and systolic pressures. The petechiae which are visible to the naked eye within a circle 5 cm in diameter drawn on the flexor surface of the forearm with the center 4 cm below the bend of the elbow are counted after fifteen minutes. The test is considered positive if more than ten petechiae appear Other tests for capillary fragility based on pinching [illegible] suction [illegible] or perfrigeration with ethyl chloride[illegible] have not become as widely used as the simple tourniquet test Madison and Squier[illegible] and many other investigators consider a positive Leede Rumpel test a pathological finding of significance These authors found the test positive in scurvy severe infections malignant hypertension ovarian dysfunction allergic reactions in the final phase of some malignancies and especially in primary blood diseases. Intradermal injection of 0 1 or 0.2 c.c. of a 1 3000 solution of dried moccasin venom is another method for gauging the capillary resistance.[illegible] *The test is positive when a hemorrhage of 1 cm or more in diameter appears within one hour at the site of injection*

[illegible] Koschewnikow P W Zur Frage der Brüchigkeit der Blutgefässe der Haut, Arch. f Dermat. u. Syph 167 [illegible]-460, 1933

[illegible] Hammer F Hämorrhagische Krankheiten, Handb d Haut u. Gk. [illegible] 513-543 [illegible].

[illegible] von Borbély F Ueber die Blutungsbereitschaft der Haut, München. med. Wchnschr 77 [illegible], 1930

[illegible] Kromeyer E Allgemeine Dermatologie oder Pathologie der Hautkrankheiten, Berlin, 1896 Gebrüder Borntraeger

[illegible] Cutter J B and Johnson C H Capillary Fragility A Device for the Study of Capillary Hemorrhage J A M A 105 505 1935

[illegible] Barragán, A New Sign of Capillary Fragility Elicited by Ethyl Chloride Perfrigeration Use in Case of Orthostatic Purpura Riv di clin med 41 263-271, 1940; Ibid. 394 418.

[illegible] Madison, F W and Squier T L Bleeding Due to Capillary Defect, Wisconsin M J [illegible] 31-34, 1940

4 *Clot retraction time* The clot normally separates from the serum in thirty to sixty minutes. If the platelet count is lower than 70 000 no or incomplete clot retraction occurs.

5 *The platelet count* The normal platelet count is 250-500,000

These relatively simple tests are sufficient for the vast majority of cases. For chemical assays of blood components which participate in the process of coagulation see Quick. [illegible]

Hemophilia

Hemophilia is a hereditary constitutional lifelong disease characterized by severe bleeding on relatively slight trauma It becomes manifest only in the male although the daughters of a patient are able to transmit the disorder to their sons. Besides dangerous and often fatal hemorrhages following injuries hemorrhages into body cavities especially joints are common while spontaneous hemorrhages into and from the mucous membranes do not belong to the typical syndrome Lasting deformities from hemarthrosis are usually present after the age of ten [illegible]

The typical laboratory findings in hemophilia are prolonged coagulation time sometimes of more than 48 hours while the platelet count the clot retraction and the bleeding time (from puncture or small incision) are mostly normal It seems contradictory that the bleeding time from small cuts is normal according to most authors and that at the same time the blood needs so much time to coagulate This is explainable by the intact capillary constriction and by the fact that hemophilic blood still clots a little when passing over hemophilic tissue.[illegible]

The presently accepted explanation for the pathogenesis of hemophilia is *the resistance of the platelets to disintegrate and to release the thromboplastin* This in turn prevents the release of the prothrombin which is needed for clotting Why the blood platelets are so resistant is unexplained [illegible] A vascular factor consisting of pathological vasodilatation on slight stimuli (Ricker after Gottron[illegible]) may play a part.

Dermadromes.—In contrast to other hemorrhagic diseases hemorrhagic skin lesions are not a dominant feature. There are usually no petechiae and the tourniquet test is negative except during bleeding phases.[illegible] The patients bruise more easily than normal persons and occasionally show large ecchymoses which require a long time to disappear [illegible] Small bruises in hemophiliacs tend to have a hard raised blanched center surrounded by discoloration [illegible] Such ring-shaped suffusions may become concentric rings if the central bleeding recurs. If it stops the periphery may continue to extend into the surrounding tissues. Large hematomas of the scalp are often seen It has already been mentioned that small skin wounds do not bleed excessively Even minor operations like lancing

[illegible] Birch, C L Hemophilia, Illinois Medical and Dental Monographs No 4, University of Illinois, 1937

[illegible] Émile-Weil, P Hémophilie Nouveau traité d médecine Publié par G H Roger Fernand Widal and P J Teissier vol IX, Paris, 1927 Masson & Cie

[illegible] Bulloch and Fildes Hemophilia Treasury of Human Inheritance, Galton Laboratory University of London, Parts V and VI Sec XIVa, London, 1911 Cambridge University Press.

of an abscess have been done without excessive bleeding However circumcision tooth extractions small furuncles, vaccination pustules, blows on the nose and biting of the tongue have often caused serious or fatal bleeding Small injuries in the mouth may develop constantly growing clots which fill the whole mouth and protrude like a huge tongue Similar growing clots can be seen on the skin. A rare incident is dry gangrene of a foot with spontaneous amputation without bleeding as seen in the case of a boy [illegible]



Fig 227 — Hemophilia. A small furuncle was followed by depleting hemorrhages which lasted for five weeks The picture shows the crust eight weeks later. (Courtesy Dr O L Birch and University of Illinois Press. Monograph on Hemophilia)

According to some older authors the hemorrhagic tendency decreases in the adult age but the majority of the hemophiliacs bleed to death in childhood sometimes at birth from the umbilical cord. More recently the decrease of the hemophilic tendency in advanced age has been denied.[illegible] Periods of in-

creased hemorrhagic tendency sometimes alternate with almost normal periods Spontaneous hemorrhages frequently recur in cycles of three to six weeks. Spontaneous hemorrhages have occurred in the early spring less severe ones in the



Fig 335 —Hemophilia The patient suffered small cu in the mucous membrane of the lip A day later he began bleed and continued for eigh days. The swelling of the lip and the large clot made it impossible for the patien to ea so that he had t be fed liquids through syringe inserted into his mouth and directed toward the hard pala The passage of nasal tube is dangerous procedure in hemophiliac Courtesy Dr G L Birch and University of Illinois Press Monograph on Hemophilia)

fall Hemorrhages may continue for days and weeks with tremendous loss of blood The immunity of women is probably not an absolute one since a hemorrhagic tendency especially from the uterus has been claimed in some females[334]

Émile-Weil Opitz and Zweig after Gottron [illegible] see review of older evidence in Bulloch and Fildes) [illegible] Birch [illegible] gives a long list of 'bleeding' females of hemophilic families but she considers none of them as a true case of hemophilia.

No effective treatment of hemophilia is known but injections of blood, plasma human and animal serum and human placental extract may tide the patient over a critical period Several substances have been prepared from blood



Fig 329 Hemophilia Gangrene of the foot which followed an extensive hemorrhage [illegible] the right lower abdominal [illegible] all and the entire right leg The foot [illegible] later sloughed [illegible] without the loss of a single drop of blood Courtesy Dr C L Birch and University of [illegible] Monograph on Hemophilia

and plasma which are able to decrease the clotting time of hem[illegible] Nateina Llopis a vegetable vitamin and calcium phosphate [illegible] praised has been little heard of during the last fifteen years. Many [illegible] remedies have had the same fate Pressure applied to a wound tends to [illegible] the surrounding subcutaneous hemorrhage [illegible] Several hereditary [illegible] resembling true hemophilia but differing either in heredity or [illegible] clinically [illegible], have been described They are all of little dermatological [illegible]

Pseudohemophilia is a rare hereditary disease which unlike true hemophilia occurs in and is transmitted by both sexes The disease may be carried without manifestation

The symptoms are like those of hemophilia but mostly milder especially later in life The condition may disappear as the patient grows older Epistaxis, easy bruising and ecchymoses are common but purpura and petechiae have not been seen [ ] Macfarlane[ ] has shown in capillaroscopic photography that



Fig 230.—Hemophilia Extensive hemorrhage after [illegible] furuncle of the right cheek (Courtesy Dr O L Birch and University of Illinois Press Monograph on Hemophilia.)

the capillary loops are partly distorted and do not retract after puncture so that bleeding continues in spite of normal blood platelets, coagulation time clot retraction and tourniquet test The bleeding time is prolonged.

Hereditary (familial) purpura simplex is much more common than hemophilia It is more often found in women than in men The platelet counts the bleeding coagulation and clot retraction times are mostly normal but the

[ ] Minot G R A Familial Hemorrhagic Condition Associated With Prolongation of the Bleeding Time Am J M Sc 175 301 1928.

tourniquet tests are often positive.[3837-3841] The skin manifestations are mainly spontaneous ecchymoses.

In *afibrinogenemia* (pseudohemophilia of the German literature)[3842-3844] an extremely rare anomaly characterized by lack of fibrinogen in the blood all hemorrhagic symptoms of hemophilia including fatal hemorrhage may occur. Coinsized ecchymoses around the big joints have been noticed and the patients bruise easily. The blood does not coagulate except on addition of fibrinogen.[3844]

Osler's Disease

Rendu-Osler-Weber's disease is a well-defined syndrome which is also known as angiomatosis hereditaria hemorrhagica.

H. I. Goldstein[3845] showed in a series of analyses of the accumulated material that up to 1931 about 110 families had become known in which more than 650 cases of the syndrome occurred. Since then the number of published cases has become larger. There is much discussion about the priority since many cases belonging to the condition had been published before Osler who recognized the triad of telangiectasis, hemorrhage and heredity.[3846]

The first visible telangiectases hardly appear before the age of twenty. They appear in crops with a certain predilection to the cheeks and lips. Since the individual lesions rarely disappear spontaneously their number grows with the age of the patient and may reach several hundred.

There are several types of telangiectases. Some of the smaller ones show pulsation under weak glass pressure but most of them are venous.[3847,3848] There are also small red hemangioma-like papules with or without surrounding dendritic vessels. These lesions cannot be blanched by pressure.

The telangiectases develop on the mucous membranes too. The nasal cavity, the tongue and the gums are almost always involved. Hemorrhages have been observed from almost all mucosae: from the vagina, the uterus, the bladder, the rectum and other parts of the colon, from the stomach, the bronchi and the larynx, but the nasal septum is by far the commonest source of dangerous

[3837] Witts, L. J. The Hereditary Haemorrhagic Diathesis, Guy's Hosp. Rep. 82: 465-474, 1932.
[3838] Davis, E. Hereditary Familial Purpura Simplex, Lancet 1939 2: 1110-1114.
[3839] Davis, E. Hereditary Familial Purpura Simplex. Review of 27 Families, Lancet 1941 1: 145-146.
[3840] Bailey, F. R. and McAlpin, K. R. Familial Purpura, Report of Two Cases, Am. J. M. Sc. 190: 363-366, 1935.
[3841] Rosling, E. Ueber hereditäre hämorrhagische Diathesen, Acta med. Scandinav. 72: 104-112, 1929; Ibid. 83: 231.
[3842] Rabe, F. and Salomon, E. Ueber Faserstoffmangel im Blute bei einem Falle von Hämophilie, Deutsches Arch. f. klin. Med. 132: 240, 1920.
[3843] Opitz, H. and Frei, M. Ueber eine neue Form der Pseudohämophilie, Jahrb. f. Kinderh. 94: 374, 1921.
[3844] Macfarlane, R. G. A Boy With No Fibrinogen, Lancet 1938, 1: 309.
[3845] Goldstein, H. I. Hereditary Multiple Telangiectasia. Goldstein's Heredofamilial Angiomatosis With Familial Hemorrhages (Rendu-Osler-Weber Disease), Arch. Dermat. & Syph. 26: 282-309, 1932.
[3846] Barrock, J. J. Hereditary Hemorrhagic Telangiectasia, Wisconsin M. J. 43: 806, 810, 1944.
[3847] Weber, F. P. Haemorrhagic Telangiectasia of the Osler Type. Case, Brit. J. Dermat. 48: 182-183, 1936.
[3848] Pardo-Castello, V. and Fariñas, E. P. Hereditary Multiple Telangiectasia, Arch. Dermat. & Syph. 39: 1028-1034, 1939.

hemorrhages. Death either during the attack of untractable epistaxis or by severe secondary anemia caused by the repeated attacks has often been reported but cases without the dangerous hemorrhagic tendency are known [2340] Heredity is the third characteristic of the syndrome Unlike hemophilia the condition is not sexbound and it is transmitted by both sexes following a dominant pattern of heredity

Besides changes caused by secondary anemia the *blood* findings are normal especially with regard to bleeding and coagulation time The affected capillaries have lost their contractility on injury [2344] Splenomegaly and swelling of the liver occur frequently [2339, 2342] Scherer[2343] observed cirrhosis of the liver in both mother and daughter with Osler s disease This is interesting in view of the vascular spiders which are common in hepatic cirrhosis.

Capillaroscopy reveals excessive richness of surface capillaries and lengthening or tortuosity of the loops [2341] Bommer saw aneurysms in great number but never in the retina.

The histology shows the weakness or hypoplasia of the connective and elastic tissue explaining the bulging and vulnerability of the small vessels. The condition must be considered as a systemic, hereditary disorder of the entire connective tissue system [2344]

The therapy is mainly limited to the destruction of the individual lesion by cautery This operation reportedly often fails to stop the bleeding Houser[2345] and Fitz Hugh[2342] advise against blood transfusion if spleen and liver are enlarged

In several patients with Osler s disease some of the telangiectases of the mucous membranes were seen to diminish or disappear entirely on treatment with moccasin venom [2346]

Thrombocytopenic Purpura

Thrombocytopenic purpura is also known as morbus maculosus haemorrhagicu or Werlhof's purpura Its main feature is abnormal bleeding which may occur in any organ the skin almost never being spared All mucous membranes especially those of the nose the mouth the lungs the genitourinary and the digestive tracts may ooze blood in varying degrees of severity Cerebral and adrenal hemorrhages occur The onset is often sudden without any premonitory symptoms. The course may be hyperacute acute chronic or intermittent The disease may terminate in complete restitution or in death from hemorrhage or from aplastic anemia caused by the repeated attacks. No

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[2339] Milbradt W Erfolgreiche Lebertherapie bei einem Fall von Teleangiectasia haemorrhagica Hereditaria (Osler Disease) mit Leberstörung Arch f. Dermat Syph 166 34-40, 1932.

[2340] Milbradt W Atypische diffuse Sklerodermie mit Oslerschem Syndrom und Leberstörung Dermat Wchnschr 99 973-979 1934

[2341] Rosenthal Oslersche Krankheit, Kbl 40 720 1932

[2342] Fitz-Hugh, T J Splenomegaly and Hepatic Enlargement in Hereditary Hemorrhagic Telangiectasia, Am J M Sc 181 261-268 1931

[2343] van Bogaert, L and Scherer H J Hémangiomatose familiale de Rendu-Osler et cirrhose hépatique Ann de méd 38 290-300, 1935

[2344] Rosenthal F and Unna, P Ueber das Wesen der Oslerschen Krankheit Klin. Wchnschr 12 845-848, 1933

[2345] Houser K. M Hereditary Hemorrhagic Telangiectasia, Ann. Otol. Rhin & Laryng. 43 731 738, 1934

age is immune but children and adolescents especially girls in puberty are more likely to become afflicted and their cases are more often acute. The typical blood findings are low platelet count and increased bleeding time up to ninety minutes. The coagulation time is normal or only moderately increased but the clot does not retract. The coagulated blood remains in a jelly like condition. The tourniquet test is positive. Anemia and abnormalities of the leukocytic picture are absent.[3a4] The spleen is often enlarged and tender

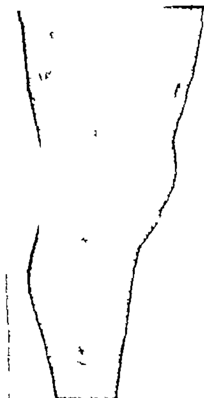


Fig. 831 —Thrombocytopenic purpura. Allergy ... (Courtesy Dr. Erich Urbach.)

Thrombocytopenic purpura is either an entity of its own the cause of which is unknown or it is caused by a known factor such as infection blood dyscrasia poisoning or liver disease. E. Frank called the idiopathic type essential thrombopenia (thrombocytopenia) to separate it from similar hemorrhagic diseases secondary to other conditions. There is no dermatological difference between these two groups. Essential thrombocytopenia is a rare disease. Only about 179 cases were counted in 275 000 admissions in two American and one European hospitals.[387] These figures probably include some secondary cases. The belief is gaining ground that only the shortcomings of the present diagnostic means create what is known as essential thrombopenic purpura.

[387] Rosenthal N. Course and Treatment of Thrombopenic Purpura. J A M A 1933 101 106 1933.

Dermadromes —The cutaneous purpura appears in crops of varying abundance and on slight local trauma. A ready tendency to bruise particularly over the shins and knees is often the first intimation of the disease [194]. The purpuric spots frequently appear first on the legs and they may be restricted to the legs in less severe cases. More often the crops gradually cover the whole body. Petechiae and suffusions are usually seen simultaneously. The mixture of both types of hemorrhagic lesions in the same patient is considered a characteristic feature of the morbus Werlhofii but this should not be taken too literally. Some cases at least at certain times, show only mucosal lesions. The fresh suffusions are not always purely hemorrhagic. When they appear they sometimes have an *urticarial* character being pink and elevated and show their hemorrhagic nature more clearly only later. Such cases which are on the border line of the anaphylactoid form of purpura are rare. They may be associated with edema of the ankles. Suffusions can easily be produced by gentle flicking, bumping or pinching. They sometimes appear on areas which are exposed to pressure, e g the buttocks or the shoulders. The petechiae can be provoked by increased venous pressure by coughing, pressing during a bowel movement etc. They appear as deep purple, sharply outlined pin point or lentil sized spots, sometimes lined up in streaks from scratches.



Fig 332 — Acute purpura with thrombocytopenia

Change from the horizontal to the upright position may produce purpuric lesions. This phenomenon known as orthostatic purpura is often marked in patients who are just recovering from an attack of thrombopenic purpura. It can be observed in other types of purpura too.

Purple or black spots or suggillations especially of the gums and of the oral or pharyngeal mucosa are quite common [illegible] This diapedetic bleeding from the mucous membranes may create a very serious condition

Pathogenesis.—Thrombopenia and abnormal bleeding are the outstanding signs of Werlhof's disease Since the blood platelets are born in the bone marrow and die in the reticulo-endothelial system especially the spleen their population in the blood can be influenced from both ends. Depression of the bone marrow by bacterial and other poisons by radiant energy carcinomatosis and other local processes may thus result in the same thrombopenic and purpuric effects as hyper activity of the spleen The spleen may be thought of as devouring the platelets or as exerting a depressing influence on the megakaryocytes in the bone marrow possibly by means of a hormonal mechanism. (For discussion of the experi mental evidence see Quick[illegible]) It has long been observed that however striking the thrombopenia in Werlhof's purpura may be no definite parallel between platelet count and purpura exists. Sometimes bleeding occurred in moderate thrombopenia, and in some cases purpura did not appear with very low platelet num bers,[illegible] or the platelet count decreased only after the hemorrhage [illegible] Mac farlane[illegible] showed in capillaroscopic photographs that the injured capillaries did not retract in thrombopenic purpura. These and many other observations show that the vascular reaction more precisely the lack of vasoconstriction after injury is an important factor Quick[illegible] tried to connect the platelet and the vascular theories. The capillary dilation is caused by histamine and one of the functions of the platelets is to remove this agent which is formed in excess In carrying out this task the platelets are rendered more susceptible to agglutina tion and lysis. This hypothesis which is based on considerable evidence would explain vasodilation as well as loss of platelets. The spleen or the reticulo-endothelial system is possibly a major source of the histamine which kills off the platelets The opinion that allergy plays a part in thrombopenic purpura is gaining favor and is expressed in the tendency to remove the borderline between thrombopenic and nonthrombopenic purpura. The main reasons for an allergic theory of thrombopenic purpura are based on the great number of cases which have been observed after prolonged and repeated medication with arsphenamine gold[illegible] sedormid [illegible] quinine nirvanol and after ingestion of cow's milk[illegible] and other foods. Infections for example pertussis have caused thrombopenic purpura so have blood transfusions.[illegible]

[illegible] Watson-Williams, E The Faucial Lesions of Purpura, J Laryng & Otol 53 181 186, 1938
[illegible] Roskam, J Purpuras hémorragiques et thrombopénie. (Étude expérimentale) Pathogénie du syndrome hémorragique engendré par l'administration de sérum antiplaquettes, Sang 8: 170-169 1934 Ibid 484 400
[illegible] Hudson, E H Purpura Haemorrhagica Caused by Gold and Arsenical Compounds. Two Cases, Lancet 2: 74-77 1935
[illegible] H ber H H Purpura From Sedormid, J.A M.A 113: 874-878, 1939
[illegible] Landsberger M. Purpura nach K hmilch, Ztschr f Kinderh 39: 545, 1925
[illegible] Brinckner H N Morbus Werlhofii mit allergischer Reaktion of mütterliches Blut der gleichen Blutgruppe Ztschr f Kinderh 61 466-478, 1931
[illegible] Squier T D and Madison, F W Purpura and Food Allergy J A M.A 106: 402, 1936.
[illegible] Patek A J J Thrombopenic Purpura and Other Hemorrhagic Diseases, Am J M. Sc. 191 722, 1936

No matter what the final conception of the pathogenesis of hemorrhagic purpura will be, the importance of the capillary factor is established.

Treatment.—The most important step toward successful treatment is to find out whether there exists a causal infection, poisoning, blood-dyscrasia or malignant disease which may be treated. In the remaining idiopathic or essential cases the tendency to remissions and spontaneous healing make an evaluation of any therapeutic procedure in thrombopenic purpura difficult. However, since Kaznelson[illegible] in 1916, based on E. Frank's work, first advocated splenectomy the number of successful operations has become so large that the method is now generally considered the only means that can be relied upon when all other therapy fails.[illegible] Many large series have been reported so that the error from spontaneous healing[illegible] is now small. The postoperative mortality is seven per cent[illegible] to ten per cent[illegible] in chronic cases. In Pemberton's series of fifty-seven operations (Mayo Clinic) sixty-three per cent were permanently cured and almost all the others improved. Pemberton[illegible] feels that splenectomy is indicated in the moderately severe cases with a definitely established diagnosis. Early and mild cases do not need splenectomy. They can be treated with blood transfusions and small doses of x-ray to the spleen. However, splenectomy, if indicated, should not be delayed too long[illegible] because the operative danger increases as the condition of the patient becomes weaker. Most authors advise against splenectomy in acute cases. Kondoba[illegible] in a review of 168 cases estimates the postoperative mortality in acute cases to be as high as 20 to 30 per cent and in juvenile patients of the acute group 35 to 50 per cent. Three out of four patients with acute thrombopenic purpura who had splenectomy died, but four other patients of the same category who were treated with blood transfusions only died too.[illegible] The postoperative mortality has come down to 13 per cent in the acute cases (Brown and Elliott after Quick[illegible]) but splenectomy in children must still be considered as very dangerous. Smears from extirpated spleens usually do not show pathologic changes. Only occasionally are the splenic blood platelets increased.[illegible]

X-ray treatment of the spleen has a hemostatic effect in many types of hemorrhagic disease. Considering the relatively high mortality of splenectomy, especially in juvenile and acute cases, this method deserves a trial. In a review of 45 cases treated with x-ray, Vaughan[illegible] found 25 cures and 20 failures. About 25 per cent of the cases were acute ones which were almost all listed as cured.

[illegible] Kaznelson, P.: Verschwinden der hämorrhagischen Diathese bei einem Falle von essentieller Thrombopenie (Frank) nach Milzexstirpation. Splenogene thrombolytische Purpura, Wien. klin. Wchnschr. 29: [illegible], 1916.

[illegible] Jones, H. W., and Tocantins, L.: The Treatment of Purpura Hemorrhagica, J. A. M. A. 100: 83-88, 1933.

[illegible] Eliason, E., and Ferguson, L. K.: Splenectomy in Purpura Hemorrhagica, Ann. Surg. 96: 80-[illegible], 1932.

[illegible] Pemberton, J. de J.: The Diagnosis and Treatment of Purpura Hemorrhagica, Am. J. Surg. 24: 793-806, 1934.

[illegible] Kondoba, A.: Zur Behandlung der essentiellen Thrombopenie, Arch. f. klin. Chir. 180: 794-806, 1934.

[illegible] Marzullo, E. R.: Treatment of Purpura Hemorrhagica. Report of 22 Cases, Am. J. Surg. 22: 63-65, 1933.

[illegible] Vaughan, J. M.: Treatment of Thrombocytopenic Purpura, Brit. M. J. 2: 842-845, 1937.

Other reports are inconclusive because of small numbers or not comparable because of great differences in technique.

Rudisill[illegible] and also Mettier and Stone[illegible] believe that roentgen radiation is valuable (8 cases) in thrombopenia Doses at 200 r per sitting applied to the spleen with low intensity and heavy filtration are recommended About six treatments may be given with three days interval. The platelet count has been seen to rise after the first treatment Most of the chronic cases are now operated upon the cases with poorer prognosis being left to other methods.[illegible] X ray therapy is less reliable than splenectomy but practically without danger It may well tide a patient over a critical phase.

Blood transfusions are of great but only palliative value. Rosenthal[illegible] sees no value in repeated small transfusions. Vitamins C and B parathyroid extracts and Stryphnon[illegible] have been advocated Mocassin snake venom[illegible] is of some palliative value in chronic cases.[illegible]

Schonlein Henoch s Non thrombocytopenic o Anaphylactoid Purpura

After separating the thrombocytopenic purpura a group of purpuras remain which—though not without exceptions[illegible] has normal platelet count normal bleeding and coagulation times and normal clot retraction Usually the tourniquet test is positive.[illegible] Allergy and infection have been increasingly found to be significant in their pathogenesis. The combination with other symptoms which are well established allergic phenomena like urticaria angioneurotic edema and swelling of the joints is reflected in the term anaphylactoid.[illegible] Today the group would probably be called allergic purpura However there are many cases in which no allergic o infectious cause can be detected

In *Schonlein s purpura* as the anaphylactoid purpura has been and still is called the urticarial component is a characteristic feature. Glanzmann[illegible] used the term purpura urticaria for raised white or pink, small o large wheals. The petechiae ften de elop within the urticarial and slightly inflammatory lesions While the urticarial element quickly disappears, the hemorrhagic part stays and undergoes the well kn w n changes

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[illegible] Rudisill, H Jr Successful Treatment of Essential Thrombopenia With Hemorrhage by Roentgen Rays. J A M A 107: 2110-2130 1936.

[illegible] Mettier S R and Stone R S Effect of Roentgen-Ray Irradiation on Platelet Production in Essential Thrombocytopenia. Am J M Sc 191 794-807 1936

[illegible] Hippe H and Kortmann R Die Behandlung der thrombopenischen Purpura im Kindesalter mit Röntgenbestrahlungen der Milz. J krb f Kinderh. 139: 302-309 1933

[illegible] Wintrobe M M Hanrahan E M J and Thomas C B Purpura Haemorrhagica With Special Reference Course and Treatment, J A M A 109 1170-1176, 1937

[illegible] Bistolfi, S La roentgenterapia nelle malattie sindrome emorragica, Radiol med 19: 772-[illegible] 1932

[illegible] Dirk W Ueber die Anzeigen zur Röntgenbehandlung bei Kinderkrankheiten und über die Erfolge derselben II III München med Wchnschr 1931 II 1219 1932

[illegible] Klima R Neue Behandlung von thrombopenischer Purpura Klin Wchnschr 1936 I [illegible]-937

[illegible] Peck S M and Rosenthal W Effect of Moccasin Snake Venom (Agkistrodon piscivorus) in Hemorrhagic Conditions J A M A 104 [illegible] 1935

[illegible] Goldstein, E Schönlein-Henoch Purpura. Report of Case With Review of the Literature Clin North America 12 [illegible] 1 1929

[illegible] Glanzmann, E Purpura Fulminans, Schweiz med Wchnschr 67 [illegible] 1937

Erythema nodosum and erythema multiforme like eruptions have been observed The pleomorphic character of the lesions is supposed to be an outstanding feature [illegible] The lesions appear in crops predominantly over the lower legs. Less frequently the other parts of the body are involved The face the bends of the large joints and the palms and soles usually remain free [illegible] The crops follow each other in intervals of days or weeks. Recurrences have been observed years after apparent healing

The spring of the year seems to favor the first outbreak as well as recurrences. The term purpura (peliosis) rheumatica refers to the combination of purpura with painful mostly serous exudations into the joints. They have nothing to do with rheumatic fever

Henoch s purpura is an anaphylactoid purpura with acute hemorrhagic intestinal symptoms. Heartburn epigastric discomfort abdominal colic nausea and vomiting melena constipation or more often diarrhea with bloody stools and other symptoms of acute abdominal disease are usually present and have not infrequently led to a diagnosis of appendicitis or intussusception with subsequent laparotomy [illegible] Purpuric skin lesions in acute abdominal conditions especially in children should make the possibility of Henoch s purpura enter the physician s mind There are showers of petechiae on the skin[illegible] and polymorphous skin lesions similar to those in Schönlein s purpura to which Henoch s purpura is related Unfortunately the purpura often follows the abdominal symptoms by several days which complicates the matter and explains the diagnostic errors.

The allergic character of many cases of Schönlein s and Henoch s purpura has been demonstrated [illegible] Improvement after elimination of wheat [illegible] eggs and wheat[illegible] and a number of other items like pork milk, potatoes, chicken etc. [illegible] has been observed Allergic diseases in the family hay fever infantile eczema and preceding allergic diseases are more common than one would expect [illegible] The relationship to urticaria angioneurotic edema joint swellings and the resemblance to serum sickness has often been emphasized. Accompanying infection is just as common Tuberculosis tonsillitis [illegible] scarlet fever [illegible] prostatitis (O Leary in discussion of Caro and Zeisler[illegible]) malaria tropica[illegible] may be mentioned as a few examples

Purpura fulminans is a rare fatal hemorrhagic disease which occurs in severe mostly septic infections. The patients are almost always children While infections with pneumococci as well as scarlet fever and measles have occa

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[illegible] Alperstein, B B Allergic Purpura and Acute Abdominal Symptoms, M Rec 154 316-322 1941

[illegible] Kahn I Henoch Purpura Due to Food Allergy J Lab & Clin Med 14 834-836, 1929.

[illegible] Barthelme F L Allergic Purpura, J Allergy 1 170-171 1930

[illegible] Alexander H L and Eyermann, C H Allergic Purpura, J A M A 92 2092-2094, 1929

[illegible] Eyermann C H Henoch Purpura South M J 28: 34 1935

[illegible] Cooke, H Two Interesting Cases of Purpura, Brit M J 3664 435-437 1931

[illegible] Pratt, T A and Frew H W O Purpura Fulminans Following Mild case of Scarlet Fever Brit. M J 3560 406-408, 1929

[illegible] Caro, M R and Zeisler E P Recurrent Chronic Purpura Arch Derma & Syph. 24 702-703 1931

[illegible] Burkenstein Zwei Fälle von Malaria mit Henoch-Schönlein bzw Werlhofscher Purpura, Derm 8, 265-267 1937 Zbl 57 439

sionally been followed by fulminating purpura the majority of the cases were observed in the course of meningitis.

The ecchymoses in purpura fulminans occupy large areas, e.g entire extremities and sometimes almost the whole skin These giant lesions develop very rapidly often in a few hours. The involved areas are sometimes entirely black. A certain symmetry of the purpuric lesions is striking in some cases The platelets, bleeding time coagulation time clot retraction and fibrinogen were normal in Glanzmann s case. The autopsy findings are mostly negative.[illegible] This is not the case in a group of fulminating purpuras which now can well be separated and which is known as the *Waterhouse Friderichsen* syndrome.[illegible] *Only about sixty cases have become known since* Marchand (*according to* Glanzmann[illegible]) in 1880 first observed a case of this kind. The terminology should give credit to Little[illegible] who in 1901 ten years before Waterhouse and seventeen years before Friderichsen published twelve cases, the greatest contribution of a single author

The syndrome occurs mostly in children younger than one year but it has been seen in adults.[illegible] The onset is very sudden often with abdominal pain and vomiting moderate fever and flushed face. The patient soon becomes stuporous this may be mistaken as healthy slumber [illegible] After ten to twelve hours cyanosis which may alternate with ashen gray pallor is striking In this stage showers of petechiae may appear over the whole body The purpuric spots increase rapidly sometimes under the very eyes of the observer They may coalesce and produce a blotchy appearance. On the buttocks, back and extensor surfaces of the arms they may look like postmortem lividity The rash remains until death. Rarely the petechiae stay small. According to Aegerter [illegible] no skin lesions showed in thirteen out of fifty seven cases.

Headache and other symptoms of the nervous system profound weakness, spiking temperatures from subnormal to 108°F low blood pressure and circulatory disturbances are often mentioned Cervical rigidity is usually absent Almost all patients d ed within a day or two The diagnosis *is rarely made* antemortem. Leukocytosis is mentioned in seven cases.[illegible] In two cases[illegible] the platelet counts were extremely low in two others, normal Most of the other cases do not mention hematological findings.[illegible] Coagulation and bleeding t me have been found normal several times. Hypoglycemia and elevation of nonprotein nitrogen of the blood has been described [illegible] At autopsy the out

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[illegible] Waterhouse R A *Case of Adrenal Apoplexy Lancet* 1911, 1 577-578

[illegible] Friderichsen, C Nebennierenapoplexie bei kleinen Kindern, Jahrb. f Kinderh 87:109 125 1918.

[illegible] Glanzmann, E Beitrag zur Klinik, Hämatologie und Pathologie des Syndroms von Waterhouse-Friderichsen (Nebennierenapoplexie bei kleinen Kindern) Jahrb. f. Kinderh [illegible] 40-63 1933

[illegible] Little E G Cases of Purpura, Ending Fatall Associated With Hemorrhage I to Suprarenal Capsules, Brit J Dermat 13: 445-467 1901

[illegible] Thomas H B and Leiphart, C D Septicemia and Purpura With Adrenal Hemorrhage in the Adult, J A M A [illegible] 894-900, 1944

[illegible] Aegerter E E The Waterhouse-Friderichsen Syndrome A Review of the Literature and Report of Tw Cases J A M A [illegible] 1715-1719, 1936.

[illegible] Levinson, S A W erhouse-Friderichsen Syndrome Case With Autopsy Findings, J Pedia 14 [illegible] 939

[illegible] Usher S J W erhouse-Friderichsen Syndrome Canad. M A. J 33 [illegible], 1935

standing finding in 95 per cent of the cases was destructive bilateral adrenal hemorrhage Often no adrenal tissue could be made out

It is now certain that most of these cases are caused by meningococcic infection probably with a massive invasion of meningococci into the blood stream Just as in other rashes of meningococcic disease meningococci have been found in the purpuric lesions.[[illegible]]

Purpura annularis telangiectodes Majocchi and Schamberg s disease two related purpuric skin diseases have some internal relationship (See Polycythemia)

Recently E. Davis[[illegible]] has given a statistical analysis of 500 consecutive cases of purpura This large series provides an idea of the frequency of the various types of purpura. The diagnosis of purpura simplex was made in 15 per cent Schönlein s purpura in 2 per cent Henoch s in 0 4 per cent hereditary familial purpura simplex 15 per cent primary thrombocytopenia 0 8 per cent hemophilia 0 2 per cent and pseudohemophilia familial or nonfamilial in 1 per cent The rest (63 per cent) was grouped under the many types of symptomatic purpuras in infections poisonings etc

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[illegible] M Lean, St and Caffey J Endemic Purpuric Meningococcus Bacteremia I Early Life Diagnostic Values of Smears From Purpuric Lesions, Am J Dis Child [illegible] 1053 1931

[illegible] Latteo G Su di caso di purpora fulminant Pediatria (Riv) [illegible] 373-3 [illegible] 1931

[illegible] Davis E Purpura of Skin, 500 Cases, Lancet 1943 2 160-161

CHAPTER XXXV

DERMADROMES OF INTERNAL CANCER

Internal cancer may manifest itself on the skin by *metastases* by *nonspecific dermadromes* and by *acanthosis nigricans* [illegible]

Cutaneous Metastases.– It can generally be said that only mammary cancer in advanced stages as well as occasionally after the operation of cases on the borderline of operability reach the skin frequently by direct extension by operative implantation or by lymphatic metastases.

The contiguous metastases appear as painless nodules which grow rapidly and if dense enough coalesce into large hard masses which may surround the chest wall like armor (Cancer en cuirasse) Sometimes the diffuse invasion of the skin forms an evenly red sharply and jaggedly outlined area of inflammatory cancer which is known as erysipelas carcinomatosum

Skin metastases from visceral cancers are rare probably occurring not more often than in 1[illegible] to 3 per cent [illegible]

Since there is no flow of lymph directed from the viscera toward the skin the metastases are likely to originate from a primary lesion or still more often from secondary cancers in the lungs[illegible] or in the liver This fact accentuates the *ominous significance* of all skin metastases of visceral cancer

Adenocarcinoma of the stomach occasionally produces an outcropping of hard mostly red nodes scattered in moderate numbers over the skin. Firm scleroderma-like plaques n the skin ha e also been seen [illegible] Dermal secondaries of hypernephromas prostatic or breast[illegible] ca cers, have been found in the scalp suggesting sebaceous cysts [illegible] or turban tumors.[illegible] The upper abdomen and the umbilicus have relatively often been seen to de elop metastatic growths originati g from the stomach ovary or uterus. They are direct subsidiaries of metastatic nodules in the liver from which they travel through the ligamentum teres.[illegible]

Rectal carcin mas may develop sessile or pedunculated metastases about the buttocks.[illegible] Only a few cases of cutaneous lesions from o arian carcinoma ha e been reported [illegible] Several of the cases showed firm plaques or confluent nodules in an edematous purplish brown skin which were not very suggestive of metastatic cancer The lesions resembled erysipelas or more correctly the

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[illegible] Rothman, Ueber Hautmetastasen bei bösartigen Geschwülsten innerer Organe Arch. f Derma Syph 149 [illegible]-123 1925

[illegible] Walther H E Metastases of Cutaneous Carcinoma and Secondary Skin Tumors, Schweiz med Wchnschr 71 [illegible]-1002, [illegible]41

[illegible] Gates, O Cutaneous Metastases of Malignant Disease, Am J Cancer [illegible] 718-720, 1937

[illegible] Berk, [illegible] C Epitheliome Handb d H. Gk 12, 3 [illegible]-403 1933.

[illegible] Bade W Das metasta ische Carcinom der Haut im Anschluss an Carcinom innerer Organe, Arch. f Dermat Syph 170 257 279 1939

[illegible] Reschone F Metastases of the Scalp Simulating Turban Tumors, Arch. Dermat & Syph 41 [illegible]-[illegible], 1940



Fig. 333.—Outcrop metastases from cancer of the stomach.



Fig. 334.—Skin metastases from cancer of the stomach.

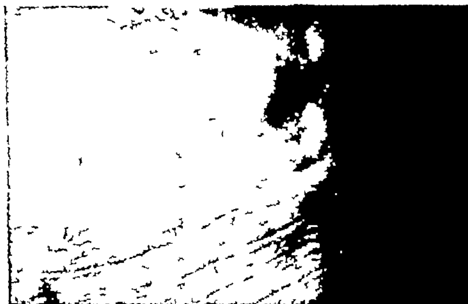


Fig. 335.—Lymphosarcoma cutaneous metastases. Forehead.



Fig. 336.—Skin metastases from lymphosarcoma.

erysipelas carcinomatosum of the breast The biopsy however revealed metastatic ovarian carcinoma Bronchial carcinomas metastasize to the skin relatively often [illegible]

A rare event is the hematogenous spread of a cancer developing from the epithelial lining of an *osteomyelitic sinus* Crops of metastatic nodules have appeared in the skin of the upper arm after the amputation of an osteomyelitic *finger* [illegible]



Fig 237 Congested veins in carcinoma of the esophagus

Lymphosarcoma and melanosarcoma are probably more apt to metastasize to the skin than the other more common cancers. They both form cutaneous and subcutaneous nodules or plaques which in some cases appear on the surface in enormous numbers The metastases of melanoma are in one out of three cases entirely or partially pigment free (amelanotic) the melanotic character of the cells being demonstrable only by the positive dopa reaction [illegible]

[illegible] Stewart, O D Obermayer M E and Woolhandler H. Cutaneous Metastatic Carcinoma Originating From Osteomyelitic Cavities *Arch Dermat & Syph* 41 544-550 1940.

Conclusions with regard to the *site of a primary* tumor from the distribution or clinical appearance of skin metastases are less reliable than the pathologic picture.

The skin does not seem to offer a good soil for the cancerous seeds. Skin nodules have been seen to disappear *spontaneously*[illegible] and they usually appear quite *radiosensitive* this can be interpreted as a lack of vitality A few hundred roentgen units may make them disappear but of course there is no more than palliative benefit for the patient from treating metastases. However it is not true that cutaneous metastases indicate a particularly fast rate of growth of the primary tumor or that they herald approaching death The patients may still live many months or even years.[illegible] Three years of life have been recorded in a case of adamantinoma of the mandible after distant metastases had appeared on the temple.[illegible] Three to six months is the average time a patient will live after the appearance of skin metastases.

Nonspecific Exanthems.—A still rarer dermadrome of internal cancer is the *nonspecific exanthem* These eruptions range from simple pruritus and prurigo-like eruptions with hyperpigmentation to bullous multiform and eczematoid rashes Typical dermatitis herpetiformis[illegible] lupus erythematosus acutus pellagroid and exfoliative dermatitis[illegible] generalized urticaria[illegible] purpura,[illegible] and purpuric dermatitis with widespread superficial necrosis are on record[illegible] Thrombocytopenic purpura[illegible] may be caused by massive invasion of the bone marrow by metastases. In some cases[illegible] a generalized polymorphous exanthem was seen in x-ray treated malignancies of the mouth and neck. Drug eruptions from barbiturates are difficult to rule out in some of these instances.

The rashes especially pruritus, may precede subjective or objective signs of cancer and they may disappear after successful removal of the neoplasms[illegible] The peculiar tendency to multiple peripheral thromboses and short clotting time in pancreatic cancer have been mentioned (see pancreas) The exanthems in internal cancers are interpreted as reactions to metastasized tumor cells which have been destroyed by cutaneous defense mechanisms.[illegible]

Diffuse deep *bluish-black discoloration* of the face neck and hands together with melanuria in a case of widespread metastases of a malignant melanoma was

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[illegible] Maury A Herowitz A and Miget A Epithéliomes métastatiques de la peau, Bull. Soc franç de dermat et syph 40: 129 1291, 1933

[illegible] Du Bois Cancer de la langue et métastases cutanées Sch eiz med Wchnschr 1928, II 1051 1060

[illegible] Kaufman-Wolf M Haut metastasen im Anschluss an Karzinom innerer Organe Arch. f. Dermat Syph 124 700-7 4 919

[illegible] Schweigl, B Erythrodermie und Uteruskarzinom Zbl f Gynäk. 87 94-99, 1933

[illegible] Urbach, E Endogenous Allergy Arch. Derma & Syph 48 687 783, 1943

[illegible] Stillman, B O Coincidence of Malignant T mor nd Purpura Haemorrhagica, M. Clin. North America 14 1433-1474 1931

[illegible] Becker S W Kahn, D and Rothman, S Cutaneous Manifestations of Internal Malignant Tumors, Arch Derma & S ph 45 1069-1080, 1942

[illegible] Blum K Ueber symptoma ische Thrombopenie bei Magencarcinom, Med Klin 24 1200-1202, 1928

[illegible] Loes L and Castel M E Exanthem Complicating Neoplastic Disease 4 Cases, Am. J Roentgenol 43 487-496 1 40

seen by Odel Montgomery and Horton[illegible] The authors assumed involvement of the adrenal glands and chromaffin tissue

The eruptive appearance of senile *hemangiomas* (ruby points) in relatively young persons has been *disproved* to be suggestive of visceral cancer[illegible] Schridde[illegible] claimed that the occurrence of dark, pigmented coarser hairs of dull surface especially on the temples but also in the eyebrows and beard were indicative of cancer They were even found among blond and gray but not among red hairs. This claim still lacks confirmation



Fig 33[illegible] —Acanthosis nigricans. (Courtesy Dr M. Jessner)

Acanthosis nigricans is a dermatosis of remarkably uniform appearance. The disease is rare about 400 cases have been recorded since S. Pollitzer[illegible] in collaboration with P G Unna published the first case in 1890 (see also Pollitzer[illegible]) The significant elements of the gross skin changes are a characteristic *distribution papillary hypertrophy hyperpigmentation and hyperkeratosis* The sites of predilection are the axillae the nape of the neck, the genitals the inner

[illegible]Odel, H M Montgomery H and Horton, B T Diffuse Melanosis Secondary to Malignant Melanoma, Proc Staff Meet M yo Clin 12: 742-747 1937

[illegible]Schridde, H Krebshaare München med W hnschr 69: 1505-1506 1922

[illegible]Pollitzer S In ernat Atlas sel Hautkr 10: 1890

[illegible]Pollitzer S Acanthosis Nigricans, J A M A 53 1369-1373 1909

thighs, the elbow bends, the umbilicus, the perianal region and the dorsa of the hands and feet. In some cases the lips, the anterior neck, the areolae of the nipples and large areas of the trunk may also be affected. There is, almost in all cases, marked symmetry provided the picture is fully developed.

The affected skin is densely covered with mostly smaller than pea-size sessile nodules with a more or less rounded top. Many of them, especially in the axillae and on the nape, are crowded into rows or small groups and separated by the natural furrows of the skin. Among the great number of little papules is scattered a much smaller number of larger ones, forming a picture comparable to the fungiform papillae among the filiform papillae of the tongue. In the folds cauliflower or cock's comb resembling growths have been observed.

The color of the lesions varies from gray, slate or yellow to all shades of brown and black. The melanosis often extends beyond the papillomatous area. Sometimes gross hyperpigmentation is missing, the lesions then having a yellow orange hue. Depigmentations within the darkened areas are due to inflammation. Scattered nevus-like, hyperpigmented lesions in apparently unaffected skin are frequent concomitant efflorescences which may appear in great numbers. Scaling, dryness, or palpable roughness, as gross expressions of hyperkeratosis, are present but are not prominent features. The palms and soles are often hyperkeratotic, but they remain free of hyperpigmentation. Pruritus is sometimes present.

The disease starts gradually, most often under the arms, and progresses slowly. The pigmentation is increased by exposure to light, the papillary hyperplasia by friction and maceration.

The oral *mucosa* and the transitional skin of the lips and of the vulva participate in the papillary hyperplasia in about one half of the cases. The dorsum of the tongue may take on a furrowed appearance resembling lingua plicata, and the papillae may be enlarged and rough like those of a cat's tongue. Even thin spines have been described. Similar papillary or granulated surfaces may be seen on the palate, the line along the bite on the buccal mucosa, the epiglottis and even in the larynx. Mucosal pigmentation is rare, but it has been observed often enough to discredit its absence as being a distinguishing characteristic against Addison's disease and other melanoses. The esophagus, the rectum and the lower part of the vagina often participate in the process.

The *hair* is usually destroyed in the affected areas.

The *nail* beds may be pigmented and the nails longitudinally grooved.

The *histopathology* reveals enlarged and elongated papillae, hyperpigmentation in the basal cell layer, acanthosis and hyperkeratosis. A small amount of inflammation is present. Hypertrophy of the sebaceous glands has been noted.

It is customary to distinguish between a *benign* and a *malignant* type of acanthosis nigricans. There is no difference in the morphology of the two types

Moncorps, C. Keratosen, Acanthosis nigricans in Handb. d. H. u. G., 8, 2: 373-403, 1931.

Kittner, H. Die Akanthosis nigricans und ihre Bedeutung für die Diagnose des malignen Tumors, Mitt. d. Grenzgeb. d. Med. u. Chir. 39: 276-306, 1926.

Tesseraux, H. Ueber Acanthosis nigricans bes. über einen Fall mit Beteiligung der Speiseröhre, Virchows Arch. f. path. Anat. 279: 253-261, 1931.

Yamada, K. A Case of Acanthosis Nigricans, Jap. J. Dermat. & Urol. 28: 61, 1928. Abst. 10, 744.

The adjective malignant refers to the association with malignancy not to a malignant course of the dermatosis itself The benign type is also often called juvenile because many cases start in early childhood and remain stationary throughout later life Some of these patients died later of cancer Some of the *juvenile cases were malignant and some adult cases at least clinically were not* associated with malignancy [illegible] Thus there is no sharp borderline between the two types The etiology and pathogenesis of acanthosis nigricans is far from being understood but there are some facts known which eventually may lead not only to the elucidation of the remarkable phenomena of this disease but also of other pigmentary disorders



Fig 330 —Acanthosis nigricans Obesity Juvenile case no malignancy (Courtesy Division of Dermatology Department of Medicine University of Chicago)

The most important etiologic fact is that at least 50 per cent of the cases of acanthosis nigricans occur in patients with cancer Fully 92 per cent of these malignancies were found in the *abdominal* viscera mostly in the stomach Almost all of the nonabdominal cancers had abdominal metastases.[illegible] The course of many neoplasms associated with acanthosis nigricans is highly malignant.

[illegible] Burgess, N A Case of Acanthosis Nigricans, Brit. J Dermat. 43 169-177 1931

[illegible] Ollendorff Curth H Cancer Associated With Acanthosis Nigricans Case Arch. Surg 47 517-553 1943

In trying to explain the peculiar pigmentary skin disease which has some features of Addison's disease the thought of an adrenal etiology has arisen. However at least twelve cases are on record in which autopsy failed to show any adrenal involvement. H. O. Curth[illegible] who has recently reviewed the available material with regard to other endocrine glands, arrives at the conclusion that theoretic considerations and actual records of cases speak against endocrine

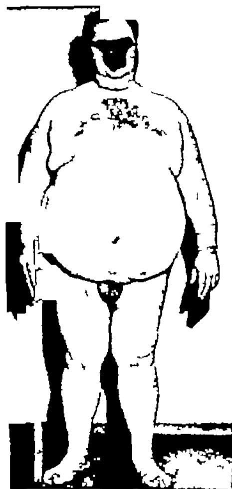


Fig. 340.—Obesity of pituitary type in patient with acanthosis nigricans. (Courtesy Division of ology, Department of Medicine, University of Chicago.)

disturbances as a causative factor in acanthosis nigricans. Yet a great number and variety of endocrine disorders have been found in association with acanthosis nigricans. It seems that although at the present time no satisfactory endocrinological etiology can be propounded the described associations with obesity, debility, dwarfism, genital hypoplasia, diabetes, goiter, cryptorchism, achondro-

plasia and acromegaly cannot be slighted Puberty exerts a provoking influence on the onset or development [illegible] Of great interest is the case of Hellerström[illegible] who observed marked though not complete regression of the diffuse papillomas after castration of a male patient Ketosteroid determinations do not seem to have been done in acanthosis nigricans. In a few cases the dermatosis subsided after treatment of the cancer and recurred with it (Spieschka after Moncorps[illegible]) Spreading of acanthosis nigricans after stationary periods seems to coincide with the development of cancer [illegible] These observations point to the neoplasm itself as a cause. But the great rarity of acanthosis nigricans compared with the frequency of abdominal neoplasms compels one to believe that a rare combination of factors must be required The same conclusion must be applied to the association with other diseases. The dermatosis usually preceded in some cases for many years the development or at least the discovery of cancer The etiologic role of the abdominal *sympathetic* system is not yet clear Stimulation of the chromaffin system could explain the hyperpigmentation but not the other aspects of the syndrome Most cases have not been investigated thoroughly from this view point In one case the resection of a cervical ganglion resulted in rapid regression of acanthosis nigricans in the axillary areas.[illegible] Ten instances of *familial* occurrence, all of the benign type have been observed [illegible]

The *treatment* of acanthosis nigricans is at best symptomatic unless regression occurs after extirpation of the malignancy The *prognosis* of juvenile acanthosis nigricans as a dermatosis is that of an incurable though in itself not dangerous, anomaly comparable to a widespread nevus However the prognosis of the juvenile benign variety is darkened by the frequent association with systemic disease The prognosis of the cases starting in the age group from 20 to 40 years is doubtful Acanthosis nigricans which develops after the age of 40 is almost certain to be indicative of cancer usually visceral[illegible] which when the dermadrome appears, already has metastasized. Exploratory laparotomy is inadvisable (O Leary in discussion to Michelson[illegible])

[illegible] Hellerström S Zur Kenntnis der Acanthosis nigricans. Act dermat —venereol 14 86-93 1933 Ibid 46 180 1931

[illegible] Mason, J C and Montgomery H Acanthosis Nigricans and Pelvic Malignancy Proc Staff Meet M yo Clin 11 113-117 1936

CHAPTER XXXVI

DISORDERS OF THE NERVOUS SYSTEM

The function of the skin as an organ of sense may become affected by disturbances of the peripheral sensory nerves as well as of the central nervous system Cutaneous secretion pilomotion vascular tonus and trophic balance depend on the autonomic nervous system the functioning of which may be disturbed by local organic lesions as well as by reflexes and hormonal activations originating somewhere else. These considerations give us an idea of the complex mechanisms by which a great variety of noxae including malformations injuries infections poisonings and endocrine disorders, may produce dermadromes of neurogenic character

Cutaneous Senses [illegible]

A variety of specialized nerve endings gives the skin the character of a sense organ The perception of all cutaneous stimuli is not diffuse as it seems to be but localized in points which are distributed over the skin in varying density The end organs related to the sensitive spots are highly specialized in their functions Thus, forcing of a needle into a Meissnerian body does not cause pain but only the sensation of touch The *warmth* spots are most dense on the face and on the lateral aspects of the fingers (2 per square centimeter) The *cold* spots are much more numerous with the greatest density on the face and on the trunk. About 11 cold spots can be mapped out on one square centimeter of facial skin [illegible] About one-third of the body surface is unable to perceive warmth

Free nerve endings in the epithelium, radiating from subepithelial plexuses, receive the stimuli causing the sensation of *pain* The skin has only one quality of pain but differences in intensity and duration may cause such varieties as burning pricking and soreness. Lewis and Hess[illegible] believe that pain is caused by a substance produced in the tissue and acting on the endings of the pain nerves. This hypothetical substance does not seem to be histamine

The pain spots are most dense in the popliteal fossa with 232 per square centimeter and least dense on the tip of the nose with only 44 per square cm [illegible] The sense of *touch* is also localized in points which are mostly situated at the hair follicles. The nerve endings surround the follicles like a basket The bent hair acts as a lever and intensifies the pressure on the end-organs. The hairs widen the perceptive area of the follicle and make the point system appear diffuse A shaved area is considerably less sensitive to touch than a hairy one [illegible] The

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[illegible] Guttmann, E. Haut und Nerven-System, Handb. d. H [illegible] Gk. 4, 2 [illegible] 1929

[illegible] Von Frey M and Rein, H Physiologie der H [illegible], Handb. d. H [illegible] Gk. 1, 2 [illegible]

[illegible] Lewis, T and Hess, W Pain Derived From the Skin. Mechanism of Production, Heart 1[illegible] [illegible]-41 1933.

sensation caused by a constant stimulus for example the bending of a hair soon fades and is no longer perceived This phenomenon is called adaptation Because of adaptation we do not feel the weight of our clothes and a needle prick is painful only for a moment The pain will stop in spite of the fact that the needle is still sticking in the skin We do not feel a temperature which does not change.

Nerve Section—The effect of cutaneous nerve section was studied in famous self-experiments by Head Foerster[2923] in evaluating nerve injuries caused by gun shots during and after the first World War and other authors[2924] modified Head's observations to some extent.[2925] The section of a sensory nerve immediately abolishes all forms of skin sensibility The areas of thermal tactile and analgetic anesthesia after section of the nerve are not entirely congruous. Section of the ulnar nerve for instance leaves a zone in part two inches in width in which only pain but not touch or temperature can be felt The disturbance of the perception of temperature is more extensive than that of touch and pain and the loss of the perception of warmth is more extensive than that of cold[2924] With the regeneration of the nerve the sensibility returns in two stages. The two stages are explained by some authors by the existence and the difference in the regeneration of two kinds of fibers.[2925] After seven to thirty weeks a markedly punctate sensibility appears with relatively wide anesthetic areas in between However the perception of intensities and the localization of a punctate stimulus is inaccurate and radiating widely from the point of stimulation The threshold for pain is high and the character of the pain is described as "sickly" meaning of an unusual quality This quality is illustrated by the peculiar sensibility of the cornea and the glans penis which normally are of similar character The author can from his own experience with a severed lingual nerve confirm the statement of Trotter and Davis (after O Foerster[2923]) that the character of the pain is different from the normal sensation of pain Only extremes of temperature are recognized in this stage The temperatures between 24 and 38°C do not cause a sensation of heat This first stage of the return of the sensibility is called protopathic sensibility[2926] It is followed by the return of the sensation of light touch of tactile localization and discrimination as measured by the ability to recognize two compass tips as two distinct points, and finally by the restoration of normal sensibility The second stage of recovery is referred to as epicritic sensibility *Complete restoration of the sensory functions may take up to two years. In skin grafts* the sensibility returns after 1 to 12 months and progresses centripetally

The section of a nerve abolishes the sensory functions in only part of the innervated area. Overlapping of neighboring innervations creates marginal hypoesthetic zones. A persistent circumscribed dermatitis may occasionally follow the section or injury of a nerve These lesions are restricted to the area supplied[2927] They have been used as evidence for a neurogenic theory of eczema

[2923] Foerster O Symptomatologie der Schussverletzungen der peripheren Nerven, Berlin, 1929, Julius Springer

[2924] Lanier L H Carney H M and Wilson W D Cutaneous Innervation, Arch Neurol 34 1-60, 1935

[2925] Rothman, S Physiology of Itching, Physiol Rev 21 357-381 1941

[2926] Head, H Sensibilitätsstörungen Berlin, 1920

[2927] Herrick, R Dermatitis Following Nerve Injury Arch Derm & Syph 26 879-881 1932

The sensibility of the skin is considerably influenced by the vegetative system. For example partial nerve section alone rarely causes circumscribed pruritus or hyperesthesia This could, however be experimentally produced by simultaneous nerve section and sympathectomy [illegible] Vitiligo and canities have often been observed in the area supplied by peripherally diseased nerves frequently with neuralgia. [illegible] This is most often seen in neuralgia of the trigeminal nerve. Zosteriform pigmentations after nerve injury are also known Paresthesias like numbness or formication give little information about the *nature of the nervous lesion* [illegible]

Nerve injury section and central destructive processes may cause *trophic ulcers* The trophic, i. e the nutritional balancing influence of the nervous system cannot be denied. The much disputed and not definitely answered question of specific trophic fibers does not seem to be important any longer since the trophic effects can be sufficiently explained by the known functions of the vegetative system.[illegible] Trophic ulcers are mostly seen on the pressure points of the feet and other sites subject to trauma or infection e g hands nasal septum and the mouth [illegible] The perforating ulcer has been observed in a great variety of organic lesions e.g peripheral nerve injury or therapeutic dissection [illegible] postencephalitic states, tabes, syringomyelia, cervical rib [illegible] and others. The ulcer starts as a blister or a sinus underneath a callus. Keratosis of the edge and absence of granulations in the floor are characteristics of the fully developed lesion The size and course are variable. Keratosis and sinus formation may be excessive causing deep destruction of bones.

Itching Superficial and Deep Tickling The dermatologically most important neurocutaneous symptom is pruritus. Itching can be elicited by vibrating or constant, *subthreshold tactile stimulation i.e. tickling* [illegible] *If the stimulus* exceeds a certain threshold the normal sensation of pain or touch results, and replaces the itching sensation. Scratching relieves itching by replacing it with pain to which itching has many relations.[illegible] Anesthetic areas as a rule do not itch. Intact perception of touch and pain is usually [illegible] but not necessarily a prerequisite for the eliciting of itching by superficial tickling i. e. light stroking with a hair or wisp of wool. Thus itching or superficial tickling may still be felt if a hair is lightly run over an analgetic zone in a tabetic, when a needle prick fails to cause pain In peripheral neuritis, tickle is increased where there is intensification to all forms of adequate painful stimuli In syringomyelia, a loss of pain and tickle seem to coincide. With lesions in the *optic thalamus* there is often intensification of the response to tickling stimuli over the same side of the body on which the responses to painful stimuli are exaggerated. With lesions of the internal capsule and cerebral *cortex* which have resulted in impairment of sensibility

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[illegible] Aubrun, E A Action sécrétoire et action du sympathique dans l prurit par énervation sensitive partielle Compt rend Soc de biol 111: 81-492, 1932

[illegible] Tocunnal, L Sistema neuro-endocrino cute, Gior ital di dermat. sif. 75 373-433 1934.

[illegible] Darier J Ulcères trophiques de la bouche et des fosses nasales (mal perforant bucconasal des tabétiques) et le problème des nerfs trophiques, Ann. de Dermat. 8 97 130, 1937

[illegible] Weidman, F Cervical Ribs (in skin diseases) Arch. Dermat & Syph. 35 716, 1937

[illegible] Pritchard E A B The Clinical Significance of Variations in Tickle Sensibility Proc Roy Soc. Med 26 697 704, 1933

neither tickle nor pain sensibility is impaired both are occasionally overactive [illegible] This is explained by the assumption that the tickle sensation is conducted by the peripheral neurons to the cord where the pathways cross to the other side in the posterior commissure run through the cord and the medulla near the spinothalamic tract and are finally registered in the optic thalamus not in the cortex.[illegible] Therefore cortical depressants like morphine paraldehyde and bromine do not influence itching as much as thalamic drugs like phenobarbital.[illegible] Section of the anterolateral tract of the spinal cord abolishes tickling and itching at the corresponding level while section of the posterior tracts exaggerates these sensations and protopathic pain to which itching is intimately related [illegible]

Drugs which paralyze the sympathetic system like ergotamine tartrate or stimulate the parasympathetic system like yohimbine and muscarine seem to inhibit itching Königstein[illegible] concludes from these observations that the sympathetic system plays a part in the genesis of pruritus Pruritus seems to be closely connected with dilation of the smaller vessels. It is perhaps a response to changes in the state of permeability [illegible] The psychogenic influence is powerful This also underlines the importance of the sympathetic factors. Scratching as a prompt reflex reaction to itching is not fully developed before the age of one year [illegible] but general reactions may be seen as early as the sixth hour of life *Deep tickling* is entirely different from superficial tickling and itching though the same word is often used indiscriminately One should speak of deep tickling when the sensation is felt in deeper structures and when a considerable pressure is necessary to elicit it Von Frey[illegible] relates deep tickling to the sense of pressure superficial tickling to the sense of pain Tickling is mainly though not exclusively confined to certain areas like the anterior aspect of the neck, the armpits the abdomen and the clitoris A sensation more similar to deep tickling than to itching occurs in the mucosae too e g rectum urethra larynx and trachea A characteristic of deep tickling compared with itching is its relation to uncontrolled reflexes like laughter and other widespread muscular contractions. The erogenic effect of tickling is well known [illegible] Tickling does not elicit scratching but muscular defense

Head's hyperalgetic zones are due to the projection of visceral pain to certain segmental skin regions These regions correspond to those observed in herpes zoster Head[illegible] *mapped such skin zones for many internal organs* (see M Lewandowsky[illegible]) The validity of the phenomenon has been amply confirmed *though there are many controversies over details It should be emphasized that*

[illegible]Ehrenwald H and Königstein H Klinische und experimentelle Untersuchungen über das Juckgefühl Wien klin Wchnschr 42: 397 1929, 1929 II

[illegible] Königstein H Zur Entstehung und Bekämpfung des Juckreizes Wien klin Wchnschr 1 81 16 926

[illegible]Brack W Die Bedeutung des vegetativen Systems für die Entstehung des Juckens Deliberations I Internat Cong Dermatology Budapest 2 159 1935 Zbl 53 458

[illegible]Hartmann-Karplus D Juckempfindung, Kratzen Pilomotorenreflex im Säuglingsalter Jahrb f Kinderh 131: 140 [illegible]

[illegible]Von Frey M Ueber den Kitzel Ztschr f Aerztl Fortbild [illegible] 81-82 1935

[illegible]Dunbar H F Emotions and Bodily Changes New York, 1935 Columbia University Press.

[illegible] Dunbar H F Physical and Mental Relationship in Illness, Am J Psychiat 91:541-562, 1934.

[illegible]Lewandowsky M Die zentralen Sensibilitätsstörungen, Handb d Neurologie, Berlin, 1910 Julius Springer

Head's zones are hyperalgesias. The sensibility to touch is not increased. The diagnosis of Head's zones is made by needle pricks or by slight pinching Alterations of the sensation caused by tickling with a blunt object have been found to correspond with Head's zones. These zones of decreased rarely increased sensitivity to tickling are supposed to occur more frequently than the hyperalgetic zones. They indicate the same organ relationship [1860] A vasomotor reaction to a weak galvanic stimulus can also be used.[1861]

Herpes zoster of the corresponding region may though rarely be the only manifestation of a visceral disease e.g peptic ulcer gallstones or cardiac disease[1862] It is assumed that the viscero-cutaneous relation which consists of viscus-sympathicus—intervertebral ganglion—ramus visceralis—gray matter of the spinal cord—anterior root—spinal nerve—skin is affected in the intervertebral ganglion which probably becomes the site of the herpes zoster infection An interesting visualization of the cutaneous zone corresponding to a lung focus was observed after a weak ultraviolet radiation Only the skin corresponding to the tuberculus lung focus showed an erythema.[1861] Circumscribed edema in the viscero-cutaneous zones has also been observed [1861]

[1860] Krieger H. Veränderungen des Kitzelgefühls der Haut bei Organerkrankungen, Würzburger Abhandlungen, vol. 26, No. 6, Leipzig, 1930, Curt Kabitzsch.

[1861] Kahane, M.: Die cutane Diagnostik innerer Krankheiten, Wien. Arch. f inn Med 2 67 110 1921

[1862] Arnstein, A. Herpes zoster als einziges manifestes Symptom von im übrigen latent verlaufenden Erkrankungen innerer Organe, Wien. klin Wchnschr 34 13-14, 1921.

CHAPTER XXXVII

DISORDERS OF THE NERVOUS SYSTEM

The Autonomic Nervous System

The autonomic or involuntary nervous system innervates the sweat glands the musculi arrectores pilorum and the tonus of the blood vessels probably also the secretion of the sebaceous glands. Almost every cell of the skin is surrounded by an extremely fine reticulum of sympathetic fibrils, the so-called sympathetic basal plexus or terminal reticulum (Stöhr after F John[3883])

Sweating —The innervation of perspiration has a subcortical center in the hypothalamus. From there the sudomotor impulses descend through the brain stem the medulla and a series of spinal centers, to the anterior roots and the peripheral sympathetic pathways (Walker after Rothman[3884]) A major crossing takes place in the lower pons.[3885,3886] The pathway of the sweat inhibiting action runs through the posterior roots.[3882] In spite of their sympathetic pathway the sudomotor fibers behave like parasympathetic or cholinergic nerves. Their stimulation causes liberation of acetylcholine in the skin and therefore can be suppressed by atropine and enhanced by physostigmine The formation of acetylcholin in the venous return of a perfused cat leg has been demonstrated with the eserinized leech preparation[3887]

Sympathectomy and the section of a peripheral nerve (e.g the sciatic) causes anhidrosis in the area supplied and hyperhidrosis in the surrounding margin[3888,3889] A reflective hyperhidrosis can be observed in the corresponding symmetric zone.[3890] Sweating tests are used in the diagnosis of postural hypotension and in determining the degree of completeness of sympathetic denervation after sympathectomy and removal of sympathetic ganglions.[3891]

[3883] John F Skin as Organ Controlled by Vegetative Nervous System, Med. Welt 13 935-963, 1939

[3884] Rothman, S Role of Autonomic Nervous System in Skin Diseases, Psychosom. Med 7 90-96, 1945

[3885] Pent, M M and List C F Changes of Sweating in Lesions of Pons, Medulla Oblongata, and Upper Cervical Cord, Tr Am Neurol A 64 93-96, 1938

[3886] List, C F and Pent, M M Sweat Secretion in Man Sweating Responses in Normal Persons, Arch Neurol & Psychiat 39 1228-1237 1938

[3887] Dale, H H and Feldberg W Chemical Transmission of Secretory Impulses to Sweat Glands of Cat J Physiol 82 121 128, 1934

[3888] Frölich, A and Zak, E Untersuchungen über d periphere Schweissecretion Naunyn-Schmiedebergs Arch 168 620-637 1932

[3889] Ackermann, A Studien zur Physiologie der Schweissdrüsen, Dermatologica 79 319-334, 305-332, 1939

[3890] Guttmann, L Motorische und vegetative Grenzzonenbefunde bei Laesionen peripherer und zentraler Abschnitte des Nervensystems, Z Neurol 147 291-307 1933.

[3891] Brown, G F Clinical Tests of Function of the Autonomic Nervous Systems, J A.M.A. 106 353-357 1936.

The spinal centers of perspiration and piloarrection have been mapped and tabulated by Ottfried Foerster [illegible] Central cerebral lesions may cause contralateral hyperhidrosis (hémiplégie sudorale Binger and Berg after Marchionini [illegible, illegible] This however is only marked in early lesions since compensatory mechanisms soon develop and some fibers remain uncrossed Unilateral mostly facial hyperhidrosis is seen in connection with peripheral sympathetic disturbances, mostly injuries of the parotid area,[illegible] or after thyroidectomy [illegible] Unilateral sweating is often combined with flushing facial paralysis and disturbances of the parotid gland

Ackermann[illegible] found sweat secretion to be the resultant of two antagonistic processes. In the proximal section of the gland sweat is secreted through para sympathetic impulses. In the more distal part of the tubule a regulating resorption under parasympathetic and sympathetic influences may take place [illegible]

Our knowledge of the autonomic innervation of the *sebaceous glands* is meager A well known fact is the seborrhea which sometimes follows brain lesions especially of the midbrain and pons (see section on encephalitis)

The psychogalvanic reflex, or the Tarchanoff Veraguth phenomenon is the decrease in the *electric resistance of the skin* caused by sensory stimuli and psychic excitement. The electric resistance depends on the amount of sweat and is one of the most sensitive psychosomatic reactions. Any psychic concentration emotion or effort measurably increases the perspiration The lie detectors are based in part on the increased sweat secretion under emotion. Food ingestion lowers the electric resistance

The reflex may become conditioned so that it occurs at meal time, even if no food is being eaten [illegible]

The electric resistance is high in areas which do not sweat Therefore the measuring of the electric skin resistance can be used for mapping the sudomotor innervation. The areas affected by sympathectomy offer a high resistance to the passage of a very small direct current There may be variations, from a few hundred to many thousand ohms, within less than ¼ inch. The electric skin resistance is normally lowest in a sharply demarcated area which includes both eyelids, the nose, the mouth varying portions of the forehead of the cheeks, and of the skin under the lower lip During sleep this area becomes narrowed finally consisting of only a small margin around the mouth Similar areas of low resistance exist on the palms and the soles The patterns of areas of low

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[illegible] Marchionini, A Hautkrankheiten und Nervensystem, Fortschr d Neurol., Psychiat. 6 7-[illegible] 1934

[illegible] Marchionini, A Hautveränderungen bei nichtsyphilitischen organischen Erkrankungen des Zentralnervensystems, Fortschr d Neurol Psychiat. 6 303-312, 1934

[illegible] Roger H Les syndromes sympathiques d'hémisudation faciale Riv di clin med 34 161 167 1933

[illegible] Löhlein Vasomotorische und trophische Störungen nach Läsion des Halssympathicus, Klin. Monatsbl f Augenh 87 624-636, 1931

[illegible] Wilson, W O Observations Relating the Innervation of the Sweat Glands of the Face Clin. Sc. 2 273-286, 1936

[illegible] Regelsberger H Das Electrodermatogramm und die Nahrungsreflexe des Menschen, Ergebn. d. inn. Med u. Kinderh. 48 128-165, 1935.

temperatures greater than 3° C justifies immediate amputation of a limb. The level of amputation should not show a temperature lower than 1 C below the corresponding level of the other side [3873] In diabetic gangrene the temperature may be raised therefore the skin temperature alone is not a reliable indicator for determination of the level of amputation [3874] In arteritis obliterans the feet may be warm In acute phlebitis the foot temperature is high The patient should stay in bed until the return of normal temperature.[3875] Inflammatory processes increase the skin temperature in a much wider area than the immediate neighborhood of the lesion itself This seems to indicate that not so much the increased local metabolism but rather the reflex arterial dilation is the cause of the heat in an inflamed area.

There is a rough parallelism between surface temperature especially of the foot and the basal metabolism so that under certain conditions the skin temperature may be used as a substitute or check for the usual basal metabolism test [3876] High foot temperatures are therefore not only found in hyperthyroidism but also at the end of pregnancy when the basal metabolism is usually increased *These high foot temperatures persist during lactation. In general* anesthesia the rise of the foot temperature indicates that the patient is asleep Primary or secondary sinking of the foot temperature indicates impending or existing shock.[3880]

Morphine Wheal —If the skin is punctured with a needle through a drop of morphine solution a wheal and a surrounding flare appear Absence of the wheal indicates a block of the small arteries which feed the area as encountered in Buerger s disease If the peripheral nerve is degenerated the flare may fail to appear [3881]

Raynaud s Disease

An invariable association of the peripheral vascular spasms called Raynaud s[3882] disease with an internal disorder which might cause the nervous impulses leading to the attack has not been discovered In fact some analysts[3883,3884] consider the absence of such a relation as a valuable criterion for the diagnosis of true Raynaud s disease However the abnormal sympathetic factor which leads to the circulatory changes cannot be denied Many modern writers on the subject deplore the rather careless labeling of a variety of vascular conditions as Raynaud s disease Raynaud himself being among the accused [3883,3884] Hunt [3885] in an effort to clarify the situation defines Raynaud s phenomenon '[3885] as intermittent pallor or cyanosis of the extremities, precipitated by exposure to cold without clinical evidence of blockage of the large peripheral vessels, and without or not more than skin deep nutritional lesions. However

[3880] Bierman, W The Temperature of he Skin Surface J A M A 106 1158-1162 1936.

[3881] Harthausen, H Morphine Puncture A Method for Diagnosing Affections in the Peripheral Arteries and Nerves, Acta dermat venereol 20: 506-513 1936.

[3882] Raynaud, A G M De l asphyxie locale et d la gangrène symétrique des extrémités, Thèse de Paris, 1862.

[3883] Allen, E V and Brown, G E Raynaud Disease (147 Cases) J.A M.A 99: 1472-1478 1932.

[3884] Allen, E V and Brown, G E Raynaud Disease Diagnosis, Am. J M Sc. 183 187 200, 1932.

[3885] Hunt, J H. Raynaud Phenomena, Quart. J Med 5 399-444 1936

[3886] Lewis, Th and Pickering G W Raynaud Disease Heart 16: 337-366 1934.

the time honored term Raynaud s disease defies eradication If one keeps Hunt s definition in mind there is no reason to abolish it since the term disease is often used for a syndrome or phenomenon of unknown cause

In the attack, the skin of the fingers, less often and less severe that of the toes, becomes suddenly pale and cool often painful. The skin temperature may be lowered as much as 16 7 centigrades (30 fahrenheit degrees) The volume of the involved part is decreased In this stage a needle prick does not cause bleed ing Cyanosis (local asphyxia) predominates in severer cases and may produce a blue brown slate or even black color The skin becomes white on pressure but is extremely slow in taking on the color of the surrounding area after the pressure has been released The radial pulse remains perceptible during the attack. The attack ends with a change of the color to vivid red caused by a violent reactive hyperemia. The changes are symmetrical. The sensibility is often disturbed but not abolished and the disturbances of sensitivity are, like the pain ill-defined and not limited to the area supplied by one nerve Anhidrosis or hyperhidrosis occurs Only in severe cases do trophic lesions like shallow ulcers, paronychias, and atrophy of the nails muscles and bones become apparent. In later stages the finger tips may be covered with a great number of small depressed scars. If gangrene occurs, it is usually superficial and always dry Hardly ever do areas larger than an end-phalanx become necrotic

The attack can be precipitated in many cases by immersion of the hand in cold water or by exposure to cool air or by chilling of the body by cold drinks.[illegible] Cold is the most important immediate cause although emotion also plays an important part in the precipitation of the attacks.[illegible] The trouble is predominantly found in young and middle-aged women The prognosis is usually good with respect to life, but the attacks may recur over many years. The pathogenesis of the phenomenon is still controversial Raynaud and many others after him believed that an abnormal vasomotor tone was the main pathogenetic factor Lewis (see Hunt[illegible]) produced much physiological evidence to the effect that the vasomotor tone was in order but that there was a local fault in the medium-sized digital arteries.[illegible] Several autopsies, on cases having had the disease for long periods of time, have not revealed any changes in the ar teries,[illegible] but a few instances of endarteritic alterations have been observed (Kolisch after Mucha[illegible]) Microscopic changes in the sympathetic ganglia and other nervous centers are on record [illegible] The vascular as well as the neural findings are not uniform and some are probably secondary The capillaroscopic picture during the attack is characterized by the empty and seemingly absent

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[illegible] Johnson C A. Raynaud Disease, 23 Cases, Surg Gynec & Obst 72: 898-907 1941.

[illegible] Craig J B: Raynaud's Disease Psychogenesis, Dis Nerv System 5 143-148, 1944.

[illegible] Mufson, J Raynaud's Disease, Ann. Int Med 20: 228-238, 1944.

[illegible] Hyndman O R and Wolkin, J Raynaud Disease Vascular—not Sympathetic—Disease, Am Heart J 23 535-544, 1942

[illegible] Danzigor H Ein Fall von Raynaud'scher Krankheit mit Obductionsbefund, Diss Freiburg i B 1922.

[illegible] Leriche, R., and Fontaine, R Sur la nature d la maladie de Raynaud, Presse méd 1932 II 1921 1925

[illegible] Mucha, V Die Raynaud'sche Krankheit, Handb f H u. Gk. 6, 2 273-300, 1928.

[illegible] Pallasse Desbasmes J and Armand Lésions de la chaîne sympathique dans la maladie de Raynaud, Lyon méd. 1931 II 117 184 Ibid. 441 71

capillaries and the constricted arteries. The spastic picture is followed by *atonic dilatation in the asphyctic stage but both spasm and atonia* may be seen simultaneously.[illegible] The capillaroscopic changes exceed the macroscopically changed areas. There can be no doubt that vasomotor stimuli play an important part. This is best demonstrated by the immediate success of surgical removal of the sympathetic fibers or ganglia through which the vasomotor stimuli must pass. *After sufficiently extensive sympathectomy* by one of the many suggested methods (Review and Methods see Homans[illegible] and Adson[illegible]) the vascular paralysis which follows the operation leaves the fingers flushed and no attacks occur as long as the sympathetic fibers do not regenerate.

The associated conditions which can be found in patients with Raynaud's disease are most often of functional character. In 24 per cent of a series of 147 noncomplicated cases psychoneurosis or neurasthenia was obviously a feature.[illegible] Syphilis arteriosclerosis and a number of rare diseases[illegible] have been found in connection with Raynaud's syndrome. Linenthal[illegible] described 3 cases with pulmonary fibrosis. A rare finding is a cervical rib. If this anomaly is unilateral the attacks are unilateral but intermittent in spite of the continuous cause.[illegible] Menopause,[illegible] sclerodactyly,[illegible] arsenical[illegible] and copper poisoning[illegible] are other rare combinations. Lewis and Landis[illegible] make use of the combination with sclerodactyly to support the arteritic theory of Raynaud's disease. Sellei[illegible] separates sclerodactyly (acroscleroma) from Raynaud's disease as well as from scleroderma. Combination with tetany[illegible] and calcifications[illegible] have caused speculation about a parathyroid etiology. Subtotal parathyroidectomy has not proved successful.[illegible]

Treatment —Since the paralytic hyperemia does not last the enthusiasm about the surgical approach has somewhat abated so that lately medical management has again been said to give equally satisfactory results. Johnson[illegible] stresses prevention of attacks by avoiding the thing that precipitates them.

[illegible] Adson, A. W. Raynaud Disease Results of Sympathectomy. S. Clin. North America 17 1081-1097, 1937

[illegible] Linenthal, H. Raynaud Disease, Pulmonary Fibrosis 3 Cases, New England J. Med. 227 432-436, 1942

[illegible] Mahques, J. and Leleng, M. Côte cervicale bilatérale syndrome de Raynaud unilatéral, Bull et mém Soc nat de chir 61 1073-1082, 1935 [illegible]

[illegible] Cassirer, H. Vasomotorisch-trophische Neurosen, ed 2, Berlin, 1912, S. Karger

[illegible] Werther Raynaud'sche Krankheit und Urticaria chronica papulosa, [illegible]

[illegible] Forsero, A. Raynaud Disease in Menopause Wien med Wchnschr [illegible] 1935.

[illegible] Berger Gefässstörung der Hände im Klimakterium. [illegible] 1932.

[illegible] Berens, B. O. and Poppel, M. H. Raynaud's Disease, Interstitial Calcinosis Circumscripta Associated With Scleroderma. Radiology 39 [illegible] 1942

[illegible] Simon, A. Ueber Kupferschädigungen und die Beziehung zum Raynaudschen Symptomenkomplex, Arch f Gewerbepath 2 71-80, 1931 [illegible]

[illegible] Lewis, T. and Landis, E. M. Raynaud Disease, Special Reference to Arteriolar Defects and Scleroderma. Heart 15 [illegible]-340, 1931

[illegible] Sellei, J. Akrosklerose und Raynaudsche Krankheit, Arch f Dermat u Syph 170 [illegible], 1930

[illegible] Borowsky, M. L. Die Pathogenese der Raynaudschen Krankheit, Deutsche Ztschr f Nervenh. 114 [illegible]-284, 1930

[illegible] Rhee, G. van Raynaud Disease With Calcareous Deposits, Arch., Dermat. & Syph 29 [illegible], 1934

[illegible] Walker, R. H. Calcification in Raynaud's Disease, Proc. Roy Soc. Med [illegible], 1934

Secondary anemia should be treated. Pancreatic extracts and thyroid[3709] have been advocated. Paraffin baths also have given considerable relief. The attack is best treated by immersion of the hands into warm, not hot, water.

Erythromelalgia (Weir Mitchell's Disease).—This syndrome features attacks of severe pain, redness and swelling, usually of the feet. Hyperhidrosis is usually present in the involved area. The paroxysms are sometimes precipitated by exposure to warmth and depression of the limb. Though occasionally associated with Raynaud's disease, it exhibits in many respects the opposite phenomena. Among a great number of occasional associations the connections with polycythemia (see there), Bence-Jones albuminuria, and neurasthenia must be mentioned.[3710,3711,3712]

Acrodynia (Feer's Disease; Pink Disease)

Acrodynia, though probably known and described in France under this name[3713,3714] more than a century ago, has become better understood and more sharply defined only during the present century. The names of Swift,[3715] Selter,[3716] and particularly Feer,[3717] after whom the disease is often named, designate some of the many authors who have been concerned with it.

The disease affects small children almost exclusively. According to Feer,[3717] the onset is insidious. The children are listless, irritable, sometimes vicious, and do not care to play. The facial expression is frowning, unchildlike, weary, so that "the experienced physician can make the diagnosis on the physiognomy alone," especially if the contracted eyelids are added to the picture. The sleep is disturbed and the appetite lost. Fatigue and gradually developing motor disturbances like unwillingness or inability to walk or stand, a bizarre and persistent jackknife-like position in bed with the head between the feet, general flaccidity of the muscles without atrophy, frequent light tremor, and other nervous symptoms, are essential features. Other important signs are increased pulse rate and blood pressure, high basal metabolism, high blood sugar, and high sedimentation rate. The temperature may be normal, but fever has often been observed in the beginning and during complications. Monothermia is sometimes a remarkable feature. Encephalitic features resembling parkinsonism have been observed.[3718]

[3709] Ipsen, J.: Zwei Fälle von der Raynaudschen Krankheit mit Untersuchungen der Arterien, Acta chir. Scandinav. 71: [illegible], 1932. Zbl. 48: 474.

[3710] Hirschfeld, R.: Die Erythromelalgie, Handb. d. H[illegible] Ok. 6, 200-273, 1929.

[3711] Lewis, Th.: Clinical Observations and Experiments Relating to Burning Pain in the Extremities and to So-called Erythromelalgia, Clin. Sc. 1: 175-211, 1933.

[3712] Brown, G. E.: Erythromelalgia and Other Disturbances of the Extremities Accompanied by Vasodilatation and Burning, Am. J. M. Sc. 183: 468-485, 1932.

[3713] Chardon: De l'acrodynie ou épidémie qui a régné à Paris depuis 1828, Rev. méd. franç. et étrang. 3: 51, 1830.

[3714] Péhu, M.: Acrodynie d'autrefois et acrod. d'aujourd'hui, Bull. Acad. de méd., Paris 111: 547-553, 1934.

[3715] Swift, H.: Erythroedema, Lancet 1: 611, 1914. (Letter to the editor.)

[3716] Selter, P.: Acrodynie, 43 Cases, Arch. f. Kinderh. 101: 244-282, 1937.

[3717] Feer, E.: Acrodynia in Peterman: Translation of Pfaundler and Schlossmann, The Diseases of Children, Vol. III. Philadelphia, 1935, J. B. Lippincott Co., pp. 435-446.

[3718] Morquio, L.: Ueber einen Fall von Infantiler Akrodynie, Arch. d. pediat. d. Uruguay 3: 105-110, 1932. Zbl. 43: 48.

Acrodynia takes a protracted course over many months. Complete recovery is the rule. Recurrences are rare.[3719] The mortality rate among 200 cases in Australia was 3 per cent [3720] when the patients were treated in their own homes but rose to 30 per cent under hospital care with the danger of intercurrent infection. Higher mortality rates have also been observed.[3717,3721-3722]

Dermadromes.—Dermadromes occur frequently[3723] and may at times completely dominate the picture. From the start the skin feels cold, clammy and flabby. *Sweating* to a degree which has its equal only in miliary fever weakens the patient and causes thirst. Sparse or copious miliaria rubra[3724] or micropapular follicular eruptions, soon follow the excessive sweating. The skin between the miliary papules may be diffusely bluish or red, the feature from which the



Fig. 241. — Acrodynia. Peeling. (Patient of Dr. S. E. Kohn.)

name pink disease was derived (Glubbe after Crawford[3724]). The papules may enlarge and become scaly and eczema-like. Cases of acrodynia have often been mistaken for eczema as long as the other important symptoms had been overlooked. In typical cases of acrodynia the macerated skin soon peels in large

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[3719] Pétre, M. Recidivations of Infantile Acrodynia, Sch. eiz med. Wchnschr. 71: 1207-1208, 1941.
[3720] Wood, A. J., and Wood, J. Pink Disease, Brit. M. J. [illegible]: [illegible]-531, 1935.
[3721] Ratcliffe, T. A. Acrodynia, J. Ment. Sc. 87: 548-571, 1941.
[3722] Bode, H. G. Die Feersche Krankheit im Licht der Dermatologie, Arch. f. Dermat. u. Syph. 167: 13-46, 1933.
[3723] Foerster, H. R. Erythredema Polyneuritis, Arch. Dermat. & Syph. 13: 17-33, [illegible].
[3724] Crawford, S. Juvenile Acrodynia, Eleven Cases, Arch. Dermat. & Syph. 20: 318-327, 1932.
[3725] Audeoud, H., and Betwonnas, L. 18 Cases of Acrodynia, Rev. méd. de la Suisse Rom. 59: 788-794, 1939.
[3726] Fessler, A. Hautveränderungen bei der Feer'schen kindlichen vegetativen Neurose (Selter-Swift-Feer'sche Krankheit), Arch. f. Dermat. u. Syph. 173: 283-290, 1935.

flakes or in smaller circular patches The *peeling* is particularly marked on the hands and feet so that it may be mistaken for scarlatina. Besides rashes from sweating and repeated crops of macular urticarial or multiform exanthems may occur especially on the mesial areas of the trunk,[1772] sometimes also on the extremities. Itching is most violent. Scratching and possibly trophic disturbances may cause pyodermic, ulcerative and necrotic complications. Bed sores occur quite frequently The teeth may become loose and fall out. Geographic tongue is a frequent feature.[1771] Salivation frequently adds to the discomfort and may outlast the excessive perspiration. The hands and feet show a characteristic purplish pink erythema The nose and cheeks may also be red.

The *hair* becomes dull and is often shed. The young patients often like to pull the loose hair out and the vertex frequently becomes bald.

Diffuse and focal inflammatory changes have been found in the sympathetic system so that the disease has been explained as a disorder of the vegetative nervous system and the term *pansympathitis* used [illegible]

The nature of the anatomical changes in the cerebrospinal system are still controversial [illegible] Several neurologists believe that encephalitis influencing the vegetative centers of *the thalamencephalon* plays a part. In the skin hyperkeratosis parakeratosis, intracellular edema[illegible] and inflammatory infiltrations in the stratum subpapillare with damage or loss of the elastic fibers and vasodilatation are microscopic features. Bode[illegible] described eosinophile bodies in the prickle cell layer surrounded by lamellated cells.

The disease is probably an infection of the autonomic nervous system though neither microbes nor positive animal inoculations have been demonstrated. However local accumulations of cases, a few familial cases,[illegible] the seasonal increase in winter and spring and the existence of fever inflammation and apparent but not invariable immunity after recovery make the infectious etiology attractive. Endocrine [illegible] toxic avitaminotic or chronic neurotrophic[illegible] hypotheses have been suggested. An interesting argument in favor of the in

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[illegible] Péhu, M Dechaume, J and Boucomont J L Acrodynie infantile Anatomie pathologique, Bull. Acad de méd Paris III s. 113 618-623 1935

[illegible] Péhu, M and Boucomont, J L'acrodynie Infantile Atti 15 Congr ital Pediat pp. 587-588, 1934 Zbl. Kh 229

[illegible] Péhu, M Dechaume, J and Boucomont, J Sur l'acrodynie infantile, Rev franç. de pédiat. 12: 230 276 277-310, 480-507 1936 Zbl. 84 332.

[illegible] Lourquand, O Dechaume J and Sedallian, P Tentatives d'expérimentation sur l acrodynie encéphalite spontanée du lapin. Ann de méd 41: 85-90 1937

[illegible] Clément, R Formes typiques de l acrodynie, Presse méd. II 1607 1610 1935

[illegible] Wolf L J and Davison Ch Acrodynia, J Pediat 4: 498-506, 1934.

[illegible] Deamer W C and Blaklod, G R Acrodynia, Am J Dis Child. 48 1226-1234, 1934

[illegible] Belloeq, O Ph and Meyer R Étude Clinique et Anatomo-Pathologique d une Forme grave d' acrodynie. Rév franç de pédiat. 8 495-509, 1932

[illegible] Blechmann, G Mouthaer H and Lecom e, A L'acrodynie, maladie contagieuse? Présentation de deux frères acrodyniques, Bull Soc de pédiat de Paris 31 128-137 1933.

[illegible] Blechmann, G and Lecomt A Acrodynie familiale (Trois enfants) Bull Soc. de pédiat. d Paris 33 620-623 1935

[illegible] Rietschel, H Zur Pathogenese der Feerschen Krankheit, Deutsche med Wchnschr 1932, I 723-725

[illegible] Bode H G and Schreuffer A Feer sche Krankheit Zbl 43: 381-453, 1932-1933

fectious etiology is the epidemiological and clinical relationship to acute miliary fever which has similar geographic distribution and symptomatology Its course however is much more acute and dangerous.

No specific treatment has been found Feer advocates high doses (2 mg daily) of atropine Ultraviolet light has also been found effective

Chapter XXXVIII

DISORDERS OF THE NERVOUS SYSTEM

Neurocutaneous Diseases

The common ectodermal origin of essential parts of the skin and the nervous system is reflected in some diseases which affect both systems at the same time and in the same or at least in a comparable manner These diseases have been called neurocutaneous diseases or congenital ectodermoses. The group comprises von Recklinghausen's disease (neurofibromatosis) Bourneville's disease (tuberous sclerosis of the brain) and various types of angiomatosis of the brain eye and skin

Von Recklinghausen's Disease.—Von Recklinghausen's disease is because of its frequency by far the most important member of the group The dermadromes tumors and pigmentations are the most common and striking manifestations of the disorder The tumors may appear as fibromas and neurinomas which cannot always be distinguished clinically Particularly the nature of small tumors may be doubtful In large soft fibromas a wormlike neurinomatous plexus may be palpable indicating the ill-defined clinical borderline between the two types of lesions.

The *fibromas* are usually soft (fibromata mollusca) and indolent rarely firm. They may vary in number from a few to several thousand There does not seem to be any site of predilection although the large fibromas seem to arise more often on the eyelids the buttocks and the labia majora. The tumors may range from pinhead sized nodules, to gigantic growths weighing more than 80 pounds. If such large tumors involve an extremity the term elephantiasis mollis is often used The fibromas may be flush to or raised above the level of the skin and the base may be thin or wide the tumor accordingly appearing pedunculated or sessile The covering skin is most often normal in appearance but sometimes it is pigmented leathery and warty A peculiar type is represented by fibromas which give the appearance of an empty bag of scrotum-like wrinkled soft thick skin (pachydermatocele) Such flabby tumor formations may be seen on any part of the body surface Trauma may change them into large and troublesome hematomas. The surface of the fibromas may show comedos or local hypertrichosis. The palms and soles are seldom involved Spontaneous involution is very rare[1749]

The *neurinomas* (neurofibromas) represent the second type of Von Recklinghausen neoplasms. In typical instances they are much firmer than the fibromas and tender on palpation or sometimes spontaneously painful They are often spindle-shaped or show their neurogenic origin by palpable worm or

[1749] Saalfeld, E and Saalfeld U Hamartome, Recklinghausen, etc Handb d H u Gk 12, 2 88-101 1932

plexus-like structures The neurinomas may develop anywhere along peripheral nerves or in the central nervous system and they too may reach very large sizes.

In one of the cases presented by Jones Jr and Hart[77a] the mass grew slowly from a small buttock tumor to a size which exceeded half of the entire body of the 36-year-old emaciated man



Fig. 343 —Von Recklinghausen disease

The *pigmentary* lesions of Von Recklinghausen s disease occur as large and small spots. H W Siemens[77a] emphasizes that the large spots differ from the ordinary smooth pigmented nevi. Their edges are smooth and their color is yellowish-brown while the true nevi spili have a more jagged contour and an olive shade The large Recklinghausen spots range from fingernail to palm-size the larger ones often being oval-shaped and arranged in the direction of the cuta neous lines of cleavage Their color is best characterized by the often used term café au lait The small spots resemble freckles, but their distribution is even and

[77a]Jones, E J and Hart, D Multiple Neurofibromatosis, Ann. Surg. 110: 916-939 1939.

[77a]Siemens, H W Clinical and Dermatologic Studies on Recklinghausen's Disease, Arch. f. Dermat. u. Syph. 160: 80-103, 1930.



Fig. 343.—Von Recklinghausen disease



Fig. 344. Von Recklinghausen's disease. Empty pouch. (From Hart, Ann. Surg.)

is not influenced by exposure to light.[370] The small spots may be innumerable. Pigmented spots of both kinds are hardly ever missed. They may precede other skin manifestations by many years. Ordinary and unusual nevi, e.g., the so-called bathing trunk nevus, hemangiomas, and the nevus anemicus have been noticed in a number of instances.[373,374]

The systemic character of Von Recklinghausen's disease manifests itself in the multiplicity of organic involvements. Abdominal, intestinal,[37] intra



Fig. 345.—Von Recklinghausen's disease. Giant fibroma interspersed with pseudo-cystic lesions.



Fig. 346.—Von Recklinghausen's disease. Empty pouches.

[373] Wakeley, C. P. G., and Weber, F. P.: Generalized Neurofibromatosis With Naevus Anaemicus, Internat. Clin. 1 Ser. 46: 144-147, 1936.
[374] Barton, A. D., and Inglis, K.: Neurofibromatosis With Both Cutaneous and Visceral Lesions, J. Coll. Surgeons, Australasia 3: 397-403, 1931. Ibid. 39: 452.

pleural[3778] and mediastinal[3779] neurofibromas as well as sciatic nerve tumors, illustrate some of the many rare localizations Of greater importance are the neurinomas of the central nervous system and of the intracranial nerves. A considerable part of the meningiomas, of the tumors of the spinal cord of the cerebello-pontine angle and of the acoustic nerve belong here.[3830,3781-3784]

The symptomatology of these central tumors depends on their location. The central neurinomas are usually not malignant although their site may make them extremely dangerous.

Perhaps of greater practical importance than the relatively rare central lesions, are the involvements of the skeleton Here, too the site is more im



Fig 317—Von Recklinghausen disease Enormous neurofibroma of the hip (From Hart Ann. Surg.)

portant than the size or number of the lesions which cause cystic destruction and peculiar irregularities in the growth of some long bones as a sequel to epiphyseal or shaft lesions during the growing age.[3785] Kyphosis may be an early symptom even before skin lesions are noted. Kyphoscoliosis has been observed

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[3778] Canigiani, T Die in rathorakalen Neurofibrome Röntgenprax. 3: 214-219 1931

[3779] Makstm, O Heathorne, J O and Allebach, H K Neurofibromatosis With Malignant Thoracic Tumor and Metastasis in Child, Am. J Dis Child. 37 381-390, 1929.

[3780] Antoni, N R E. Rückenmarkstumoren und Neurofibrome Anatomie und Embryogenese, München and Wiesbaden, 1920, J F Bergmann

[3781] Mosbacher F W Recklinghausensche Krankheit bei Tumor cerebri, Psychiat.-neurol. Wchnschr 1931 II 4 1-418

[3782] Mosbacher F W Recklinghausen'sche Krankheit, Fortschr d. Neurol Psychiat 3 239 1931

[3783] Helsmoortel, J J and Thiropont R. Tumeurs bilatérales de l'acoustique dans la neurofibromatose J belge de neurol. et de psychia 33 779-785, 1933.

[3784] Forster O and Gagel, O Zentrale diffuse Schwannose bei Recklinghausen'scher Krankheit, Z. Neur 151 1 16, 934.

in as many as 43 per cent of some series.[1782] Pseudarthroses of the legs cystic *destruction of the hip bones*[1783] *compression of the spinal cord*[1784] *and* osteomalacia[1785] represent some of the typical skeletal phenomena. Moderate acromegaly[1786] cutis verticis gyrata,[1787] Fröhlich s syndrome[1788,1789] adrenal symptoms[1790,1791] vagus tumor[1792] high blood calcium and potassium[1793] and many other endocrine features[1794] have been recorded without leading to a well founded endocrine theory of the pathogenesis of Von Recklinghausen s disease.[1795] In this connection the unfavorable influence of puberty and pregnancy on the production of tumors must be mentioned Psychic anomalies including all degrees



Fig. 348 —Von Recklinghausen disease. Large and small pigmented spots.

[1782]Stalman, A Nerven- Haut und Knochenveränderungen bei der Neurofibromatosis Recklinghausen, Virchow Arch f. Path Anat 289 96-120 1933

[1783]Richter W Neurofibromatosis Recklinghausen mit cystischen Veränderungen in den Hüftgelenkknochen Zbl 44 372

[1784]Miller A Neurofibromatosis, With Reference t Skeletal Changes, Compression Myelitis and Malignan Degeneration Arch. Surg 32: 100-122, 1936,

[1785]Oale, H N and Driver J R. Von Recklinghausen Disease Arch. Dermat. & Syph. 22: 733, 1930

[1786]Blotevogel, H. Die Charakterbildung der Neurofibromatose (Recklinghausen). Dermat. Wchnschr 1933 I 361 363

[1787]Rajka, E Pachydermie verticale (Cutis verticis gyrata) Morbus Recklinghausen, Zbl 46 18 1933

[1788]Rusakova, B Zur Frage der endokrinen Anomalien bei der Recklinghausenschen Krankheit, Russk. Vest. Dermat 9 2 1931 Zbl. 39: 318.

[1789]Obertländer E Zur Frage der Dystrophia pluriglandularis neurofibromatosa, Wien. med Wchnschr 1931 I 638-639

[1790]Rosenthal, D B and Willis, R. A. Association of Chromaffin Tumours With Neurofibromatosis, J Path & Bact 42 599-603 1936.

[1791]Levin, O L and Behrman, H T Neurofibromatosis—Elusive Manifestations and Internal Relations, Arch Dermat & Syph. 41: 480-503 1940

[1792]Hebner M Vagustumor bei Recklinghausenscher Neurofibromatose, Deutsche Ztschr f. Chir 237: 63-79 1932.

[1793]Marinato, Th and Meckel, P Recklinghausen Disease and Ca-Metabolism, Rev radiol. clin. 1 333-341 1932 Zbl 43 533.

[1794]Freund H Ueber endokrine Störungen bei Recklinghausenscher Krankheit, Arch. f. Dermat. u. Syph. 160: 128-143 1930

of feeble mindedness and frank psychoses[1744,1746,1747] are common Hebra believed "that all patients suffering from fibroma molluscum were mentally retarded individuals. In a modern series[1745] about one-half of the patients showed mental deficiencies.

The patients afflicted with Von Recklinghausen's disease often have a characteristic melancholic, or bored facial expression which Rille[1748] partly ascribes to changes in the facial skin. The eyes and ears participate in the morbid process in many ways There may be enormous tumors of the lids[1749] and of the



Fig. 348.—Von Recklinghausen's disease Small pigmented spots and larger pigmented moles The patient is only [illegible] years old, therefore lesions mostly small and not too numerous. (Courtesy Wisconsin General Hospital)

[1745] Hubble, D and Rogerson, C H Anxiety Alopecia Areata, Neurofibromatosis, Auricular Fibrillation Case, Brit. M. J 1 496-498, 194

[1746] Sertakovic, V Symptomatologie der Recklinghausenschen Krankheit, Obozr Psichiatr 4 167 173, 1930 Zbl. 56 775

[1747] Woringer F Maladie d Recklinghausen, Bull Soc franç. d dermat. et syph. 39 1610-1612, 1932.

[1748] Rille Der Gesichtsausdruck, ein neues Kennzeichen des Morbus Recklinghausen, Dermat. Wchnschr 1935, II 1433-1437

[1749] Knapp, A. A. Von Recklinghausen Disease: Case With Involvement of Left Eyelids, J.A.M.A. 100 494-496, 1933.

sclerae[2770] buphthalmos, changes of the retina and of the optic nerves or their surroundings[2771] and tumors.[2740]

Deafness from bilateral acoustic nerve tumors and other nervous disturbances of hearing are well known and sometimes demonstrable by roentgenographic examination of the petrous bone.[2772,2773]

The disease is hereditary though certain factors may be necessary to make the hereditary character manifest. The trouble has been seen as a concordant feature in homozygotic twins[2740,2774,2775] occurring in six generations[2777] and in as many as four siblings.[2776] Among 115 children of Recklinghausen patients 43.5 per cent were afflicted.[2777] H. W. Siemens characterizes the inheritance of Recklinghausen's disease as an irregularly dominant one. Solitary cases without apparent familial connection are not rare. Both sexes are equally affected.[2740] The tendency to malignant degeneration of Recklinghausen tumors may be familial (Hockstra after Mosbacher[2740])

The syndrome occurs in many degrees of severity. Within one family cases with all types of manifestations may be seen together with cases whose only symptoms may consist of some pigmented spots without tumors. Generally the term "formes frustes" is applied to cases with less than the four types of dermadromes: the large and small pigmented spots, the fibromas and the neurinomas. Apparently abortive cases showing very few lesions may still become severe.[2777]

The disease may be connatal but commonly comes on gradually.[2778] At certain periods, however, like puberty, pregnancy and the menopause, and after infections like typhoid and mumps, the rate of appearance of new symptoms may be stepped up. Since the lesions only come and do not go, older patients usually have more than younger patients.

The course of the disease has already been indicated. In advanced age the cases often become more progressive and changeable.[2740]

The life expectancy is generally favorable, but may be entirely changed by complications, particularly of the nervous and skeletal systems. Sarcomatous degenerations of (see Charache[2781]) tumors occurs in about 10 per cent,[2740] prob-

[2770] Mamoli, L. Caso di morbo di Recklinghausen con manifestazioni endocraniche: rara localizzazione epibulbare. A. H. Congr. Oftalm. pp. 663-678, 1932. Zbl. 48: 64.

[2771] Weber, F. P. and Dods, O. B. Recklinghausen Neurofibromatosis With Unilateral Buphthalmos and Multiple Changes in the Face and Skull. Proc. Roy. Soc. Med. 27: 633-640, 1934.

[2772] Gardner, W. J. and Turner, O. Bilateral Acoustic Neurofibromas. Arch. Neurol. & Psychiat. 44: 76-99, 1940.

[2773] Heublein, G. W., Pendergrass, E. P. and Widmann, B. P. Roentgenographic Findings in Neurocutaneous Syndromes. Radiology 35: 701-737, 1940.

[2774] Levers, H. Recklinghausensche Krankheit und cerebrales Syndrom bei einem eineiigen Zwillingspaar. Ztschr. f. menschl. Vererb. u. Konstitutionslehre 19: 721-730, 1936.

[2775] Loftis, M. L. Neurofibromatosis in Identical Twins. Arch. Dermat. & Syph. 42: 657, 1940.

[2776] Garland, A. Brothers With Neurofibromatosis. Brit. M. J. 2: 130, 1941.

[2777] Preiser, S. A. and Davenport, C. B. Multiple Neurofibromatosis and Its Inheritance. Am. J. M. Sc. 156: 507-540, 1918.

[2778] Gaté, J. and Cuilleret, P. 1 cas de maladie de Recklinghausen. Bull. Soc. franç. de dermat. et syph. 40: 255-258, 1933.

[2779] Andrews, G. C. Von Recklinghausen's Disease. Arch. Dermat. & Syph. 24: 483-488, 1931.

[2780] Sharpe, J. C. and Young, R. H. Recklinghausen's Neurofibromatosis: 31 Cases. Arch. Int. Med. 59: 299, 1937.

[2781] Charache, H. Multiple Neurofibromas With Sarcomatous Transformation and Skeletal Involvement. Arch. Dermat. & Syph. 40: 183-91, 1939.

ably even less frequently The patient dies with Von Recklinghausen s disease but rarely of it [illegible]

The microscopic structure of the neurinomas shows bandlike zones of parallel elongated nuclei alternating with zones of parallel thin fibers without nuclei. Sometimes the fibrous part is transformed into a dense finely reticular structure, with fusiform and anastomosing cells Mitoses are very rare. The growth generally has all the characteristics of a benign neoplasm Most pathologists believe that the neurinoma stems from the cells of the sheath of Schwann thus being of ectodermal origin The theory of mesodermal nature is defended by a minority an important argument being the transition into sarcomas.[illegible]

No satisfactory method of treatment is known

Many authors advise against inadequate surgical removal of tumors, because of the danger of sarcomatous degeneration [illegible] The removal of one sarcomatous growth may be followed by a distantly located sarcomatous transformation [illegible]

Tuberous Sclerosis of the Brain —(Bourneville s Disease) This is a congenital progressive and often familial condition It is characterized by epileptic seizures of varying types mental deficiency varying from queerness or feeble mindedness to severe idiocy by eye disorders, and dermadromes. The triad of adenoma sebaceum epilepsy and mental deficiency is called epiloia. The brain lesions are whitish relatively firm well circumscribed plaques and tumors. They are found in varying parts of the cortex as well as in the ventricles. In the lesions the nerve cells are widely destroyed or damaged by neuroglial proliferation and other processes among which a certain type of large cell and a tendency to calcification are prominent features. The latter and frequent hydrocephalus, are radiographically demonstrable.[illegible] Tumors resembling hypernephromas rhabdomyomas of the heart, and a variety of other neoplasms may be found. A high basal metabolism [illegible] gynecomastia precocious puberty [illegible] congenital malformations [illegible] and neurogenic mulberry shaped tumors of the retina[illegible] have been described in association with tuberous sclerosis. The disease becomes manifest in early childhood and runs a slowly progressive course. The majority of the patients die before the age of 25 years (Bielschowsky and Gallus after E. Guttmann[illegible])

[illegible] Harbitz, F Multiple Neurofibromatosis, Arch Int Med 3 32-65, 1909.

[illegible] Cushing, H and Eisenhardt L Meningiomas, Springfield, Ill 1938, Charles C Thomas.

[illegible] Orzechowski, K Neurinome Handb d N u. Ch. 22, 2: 1933.

[illegible] McNairy D J and Montgomery H Cutaneous Tumors of von Recklinghausen Disease Arch. Dermat. & Syph 51: 384-390 1945

[illegible] Kreyenberg G Delbanco E and Haack K Tuberöse Sklerose und Adenoma sebaceum, Z. Neur 123: 226-236, 1930

[illegible] Watrin, J Maigeant P and Weille, R Case of Bourneville Tuberous Sclerosis and Symmetrical Fibromatous Nevi of Face, Ann de dermat et syph. 10: 644-653, 1939.

[illegible] Ferle, H Ein Beitrag zu Histopathologie der tuberösen Sklerose Virchows Arch. f path. Anat. 278 690-700 1930

[illegible] Kufs, H Ueber den Erbgang der tuberösen Sklerose, zugleich ein Beitrag zur klinischen Diagnostik und Histopathologie dieser Krankheit Z Neur 144 562-582, 1933 Zbl. 68 349

[illegible] Van Der Hoeve J Eye Symptoms in Phacomatoses, Tr Ophth Soc. U Kingdom 52: 380-401 1932.

The disease has frequently been encountered in families, sometimes in three generations[illegible] and occasionally together with manifestations of Von Recklinghausen's disease[illegible] indicating the relationship of these two neurocutaneous syndromes which seem to be caused by unknown factors acting on the ectoderm



Fig 240 —Tuberous sclerosis (epiloia) Adenomat sebacea in typical distribution along the nasolabial folds and on the chin (From Good, O K and Garb J Arch. Dermat 1943.)

Dermadromes.—The best known dermadrome of tuberous sclerosis is the *adenoma sebaceum* of the face This dermatosis consists of more or less raised discrete hemispheric papules which are mainly arranged in the neighborhood

[illegible] Koenen, J Eine familiäre, hereditäre Form von tuberöser Sklerose, Acta psychiat. 7 813-821 1932

[illegible] Koenen, J Eine familiäre hereditäre Form von tuberöser Sklerose, Nederl tijdschr geneesk. 1931 I 731 738

[illegible] Borremans, Dyckmans, and Van Bogaert Formes hérédofamiliale, de la sclérose tubereuse, J belge de neurol et de psychiat 33 713-746 1933 Zbl 48: 406

[illegible] Werther Morbus Pringle, Morbus Recklinghausen und tuberöse Hirnsklerose, Zbl. 36 603, 1931

[illegible] Butterworth, T and Wilson, M J Tuberous Sclerosis, Dermatological Aspects, Arch. Dermat & Syph 43 1-41 1941

[illegible] Bychowski, Z Tuberöse Sklerose, Warsaw Czas lek. 8: 440-463, 1931; Zbl 80 184.

[illegible] Mukai, J Naevus sebaceus, Acta dermat (Kyoto) 17 433-478 1931 Zbl. 39: 854.

[illegible] Fuhs Naevus Multiplex Pringle, Zbl 48 15







of the nasolabial and mental folds. The symmetry is marked The size of the individual lesions ranges from a few millimeters in diameter to almost a centimeter the larger lesions being flatter and usually situated in the center of the group The papules may vary in color and firmness. In the so-called Balzer type the papules have the color of normal skin in the Pringle type, they are soft and red and in the Hallopeau Leredde-Darier type, they are small and very firm [178]



Fig 353 —Tuberous sclerosis Large fibromatous nevoid growth of the scalp. (From Good, G K. and Garb, J Arch Dermat 1943)

The pathological differences are explained by the prevalence of the sebaceous glands the vascular elements or the fibrous stroma Spontaneous regression has been observed in some cases but this is not the rule. The three types may be seen together [1793]

Nevoid slow growing pigmented *plaques* of a size which may cover for example the entire temporal area and keratofibromatous leather like plaques sometimes reaching palm-size have been described [1793,2000,2001] The lumbar region is a favorite site for such nevoid plaques and similar growths. The plaques show

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[1793] Dobkevitch, S Adénomes Nouvelle Pratiqu Dermatol Vol. VI Paris, 1936, Masson & Cie
[2000] Sachs M. D and Shaskan, D A Tuberous Sklerosis, Am. J Roentgenol. 51: 35-39 1944.
[2001] Kurtz, L. Tuberöse Sklerose, Hautveränderungen, Dermat. Wchnschr 1934, I 357-365.

pathologic changes similar to the adenomatous papules. They are not of the same diagnostic importance as the adenoma sebaceum.[illegible]

Slow growing multiple para ungual fibromas of small pea size, especially of the toes[illegible] have recently become known as a dermadrome of tuberous sclerosis. The lesions which have a keratotic top bleed easily and may become troublesome These tumors find their mucosal equivalent in lobulated fibromas of the gums.[illegible] The nail substance may appear thickened or grooved lengthwise [illegible]



Fig 3[illegible].—Adenoma sebaceum Courtesy Division of Dermatology Department of Medicine University of Chicago)

Lipomas syringocystadenomas and some of the skin lesions known to occur in Von Recklinghausen s disease ha e als been found occasionally in tuberous sclerosis.

Frequently the aden ma sebaceum makes ts appearance in the first decade of life[illegible] possibly stimulated by the same hormonal factor which causes the development of the sebaceous glands.

[illegible] Van Bogaert L, Bastiaanse F S Forme familiale de sclérose tubéreuse J belge de Neurol et de psychiat. 33 697 712, 1933 Zbl 48 404

[illegible] Kurtz, L. Tuberöse Sklerose mit Hautveränderungen (subunguale Fibrome Fingern und Zehen, Rosacea des Gesichtes und lymphangiektatische Fibrome an der Glutea) Zbl 48 730.

[illegible] Loos, H O Nagel- Haut- und Afterdrüsenkrankungen, Med Klin 36 479-481, 1940.

Angiomatosis cerebri —Hemangiomas of the brain are frequently[2773, 2995, 2996] associated with vascular nevi of the face While the nonactive nevus-like hemangiomas are apt to be found in the cerebrum the growing angioblastomas usually develop in the cerebellum. Only the former seem to have related skin lesions, while both develop eye manifestations, though of different types. The nervous symptoms usually start very early sometimes during the first months of life.[2997, 2998] Contralateral jacksonian fits vertigo tremor disturbances of the gait, and hemiplegia[2999] are the most obvious symptoms. Idiocy has also been observed [2997] The brain lesions may calcify and thus produce roentgenologic pictures[2773, 3010] consisting of whorls and sinuous deposits in the gyri of the frontal and temporal lobes. Asymmetry of the face[2773, 2995] may accompany the unilateral brain changes.

The accompanying vascular nevi mainly occupy the face They seem to be more often unilateral than bilateral They are large even enormous[3011] single



Fig 844A —Fibromas of the nailbed in tuberous sclerosis and adenoma sebaceum. (Courtesy Division of Dermatology Department of Medicine University of Chicago)

[2995] Krabbe, K H Facial and Meningeal Angiomatosis With Calcifications of the Brain Cortex, Arch. Neurol & Psychiat 31: 737 758 1934

[2996] Kufs, H Ueber heredofamiliäre Angiomatose des Gehirns und der Retina, ihre Beziehungen zu einander und zur Angiom ose der Ha Ztschr f d ges Neurol Psychiat. 113 651-686, 1928.

[2997] Meyer F Gesichtshauthämangiom und Gehirnrankenangiom, Monatschr f Psychiat. Neurol 93: 294-298 1936

[2998] Schaefer W Ueber einen Fall von halbseitigem Gehirn- und Ha thämangiom, Monatschr f. Kinderh. 50: 35-44 1931

[2999] Kreyenberg, G and Hanstag, I Hau hämangiom mit Rankenangiom des Gehirns ad Hydrophthalmus, Z Neur 153: 761 756 1935.

[3010] Schwarz, G W Vascular Tumors and Anomalies of the Skull and Brain, From Roentgenological Viewpoint, Am J Roentgenol 41: 881-900, 1939

[3011] Ironside, R and Hill D Cutaneous Naevus With Buphthalmos and Epilepsy J Ment Sc. 87 631-634, 1941

or multiple telangiectasias of port wine stain or tumor type sometimes involving the oral mucosa and even the pharynx.[illegible]

The nevi are often but not necessarily on the side of the hemangioma of the brain.[illegible]

Besides the telangiectatic lesions nevus anemicus has been recorded in several instances.[illegible] Pigmented nevus of one side of the face and ipsolateral glioma has been seen by Melrowsky [illegible]



Fig 3453B —Tuberous sclerosis Fibromas of the nailbeds with grooving of the nails. (From Noon, E B Arch. Dermat 944.)

Heredity is an etiological factor [illegible] Occasional combinations with the other neurocutaneous diseases have been reported.[illegible]

The term Parkes Weber s syndrome is sometimes used for the combination of cerebral and cutaneous hemangiomas with epilepsy and idiotism.

[illegible] Tyson, H. H Nevus Flammeus of the Face and Globe Associated With Glaucoma, Vascular Changes in the Iris and Calcified Vascular Growth in the Left Occipital Lobe With Right Homonymous Hemianopia, Arch Ophth. 8: 365-371 1932

[illegible] Ellis, R W B Trigeminal Naevus and Hemangioma of Meninges, Proc. Roy Soc Med 25 1733-1734, 1932.

[illegible] Weber F P and Harris, K. E A Case of Widely Distributed Superficial Telangiectatic Naevus Associated With Areas of Naevus Anaemicus Indications That Portions of the Cerebral Meninges are Similarly Involved, Brit J Dermat 44: 77-83 932

[illegible] Melrowsky E Halbseitiger Naevus bei einem Epileptiker (Sektionsbericht) Zbl. 40: 34

[illegible] Touraine A and Nguyen-Van-Tang Êta dysraphique familial, Bull Soc Franç de dermat et syph. 43 1859-1861 1936

[illegible] Greig, D M. Case of Meningeal Naevus Associated With Adenoma Sebaceum, Edinburgh. M. J 39: 103-111, 1932

CHAPTER XXXIX

DISORDERS OF THE NERVOUS SYSTEM

Diseases of the Spinal Cord

Cord lesions may regardless of their nature produce *pigmentations* Such melanoses in the area of the skin supplied by the injured parts of the cord have been observed after gunshot injuries during the first world war André Thomas[illegible] found an increase of the pilomotor and sudomotor reflexes in the pigmented areas which suggests that the sympathetic system plays a part in the etiology of the pigmentations The pigmentations may appear after two weeks (Simons after E. Kaufmann [illegible]) or after months or even years. Sézary[illegible] feels that the slow appearance of the lesions makes a sympathetic etiology unlikely Since *most of the cord injuries are fatal before the pigmentation has a chance to develop* observations have remained rare. Depigmentations of the skin after injuries or other lesions of the spinal cord e.g tumors have occasionally been seen [illegible] In one case there was red dermographism above and white dermographism below the level of the injury

E. Guttmann[illegible] points out that the fibers conducting the sensations of touch and position ascend directly without crossing while the pathways for the perception of warmth and pain enter a second neuron and cross to the other side This explains the fact that a unilateral lesion of the spinal cord causes a contra lateral anesthesia for warmth and pain Localized destruction of the gray matter of the cord also causes abolition of the perception of warmth and pain with preservation of the senses of touch and position This dissociation can be seen in several localized cord lesions e.g in syringomyelia hemorrhage into the gray matter and in intramedullary tumors. The sensibility above and below the level of a circumscribed intramedullary lesion may be undisturbed if no direct fibers are involved Complete transverse lesions of the spinal cord leads to anesthesia below the level of the corresponding cutaneous innervation The lowest segments, however often retain some sensibility

Status Dysraphicus.—Status dysraphicus [illegible] is a hereditary condition characterized by a great number of malformations. The name is derived from the pathogenesis of the leading anomaly spina bifida caused by failure of the embryonal closing of the raphe of the medullary groove. Funnel chest disproportion between trunk and extremities, abnormally long arms clubbed hands

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[illegible] André-Thomas La pigmentation de la peau dans les blessures et les affections de la moelle, Rev neurol [illegible] 103-105 1921.

[illegible] Bremer F W Untersuchungen zur Aetiologie der Syringomyelie Status dysraphicus Deutsche Ztschr f Nervenh [illegible] 1 1926

[illegible] Bremer F W Pathol.-anatom. Begründung des Status dysraphicus, Deutsche Ztschr f. Nervenh [illegible] 104, 1927

and clubbed feet polymastia asymmetry of the breasts and web formation are some of the stigmata. Debility epilepsy psychoses acrocyanosis cataract hypogenitalism Horner's syndrome heterochromia of the iris and other disturbances may accumulate in one individual but more often such symptoms are grouped in families.

Spina bifida occulta occurs in about 17 per cent of *all* persons a fact which has become known only with the advent of the x-ray [illegible] Lumbar nevi and circumscribed sometimes excessive hypertrichosis over the spine may indicate the underlying cleft formation



Fig 356 Trophedema [illegible] after spinal cord [illegible] and operation

Familial Trophedema.—There also exist a r lationship between status dysraphicu and the chronic *familial trophedem* of Nonne Milroy and Meige [illegible] This is a hereditary cond tion which has been observed in as many as five g nerations [illegible] though never in many members The disorder affects

[illegible] Curtius F and Lorenz I Klinisch-erbbiologische und [illegible] Untersuchungen an [illegible] Fällen von Status dysraphicus und 17 Fällen von Syringomyelie Ztschr f d ges Neurol Psychiat 149 [illegible] 1933

[illegible] Lewin [illegible] Trophödem Meige-Milroy Derm Wchnschr 96 [illegible] 1933

[illegible] Jaworsky [illegible] Trophödem und Spina bifida occulta Derm Ztschr [illegible] 1931

[illegible] Meige [illegible] Rev neurol [illegible] 1934

[illegible] Meige H Dystrophie oedémateuse héréditaire Presse méd [illegible]

Meige H [illegible] complément à l'histoire clinique d'une famille atteinte de trophoedème héréditaire Rev neurol [illegible]

the female sex more frequently than the male.[illegible] The trouble is sometimes congenital but more often it starts later in life frequently in adolescence rarely later A slowly progressive later stationary edema develops in one or both legs rarely in the arms. Painful febrile attacks have been observed to increase the edema [illegible] The fully developed lesion consists of an enormous firm edema *The skin is smooth white or bluish or with a vascular pattern and* feels cool. Folds cannot be raised. The contour of the legs is usually com-



Fig 257 —Patch of hair over spina bifida.

pletely lost A deep fold separates the leg from the foot The condition does not endanger life as shown by Meige's second report on the same case 35 years after his first presentation At the time of the second report, the afflicted woman was 75 years old without other trouble than the edema

[illegible] Moniz, E Sur le trophoedème chronique de Meige —Nouveaux cas —Considérations sur leur étiologie, Rev neurol 28 1090-1092, 1921

[illegible] Tauber E Milroy Disease, Arch Dermat & Syph. 23 1127 1136, 1931.

[illegible] McGuire, J and Zeek, P Pathogenesis of Chronic Hereditary Edema of Extremities (Milroy's Disease) J.A.M.A. 98 870-873 1932

Besides status dysraphicus hypothyroidism [illegible] hyperthyroidism [illegible] hypogenitalism [illegible] and melorheostosis Léri[illegible] have been found in association with the edema, but no definite etiology has been established. The dominant pathological feature is loss of the subepidermal elastica increase of collagenous fibers and widening of the lymphatic spaces. No effective therapy is known



Fig. 358.—Spina bifida X-ray of patien [illegible] patch of hair over lumbar spine.

Syringomyelia is much more closely related to status dysraphicus. Curtius and Lorenz[illegible] found among 17 cases of syringomyelia 11 instances of spina bifida occulta. In the families of patients afflicted with syringomyelia anomalies of the breasts and mental disorders are relatively common

Increase of neuroglia (gliosis) in the spinal cord and formation of tube-like cavities within these lesions lead to a great variety of neurological symptoms

[illegible] [illegible] A Trophoedema Meige) [illegible] 1925

[illegible] Petráček E Meige-Milroy'sche Krankheit, Česká dermat [illegible] 1931 [illegible]

[illegible] Goldschlag F Ueber eine Kombination von Trophödem Meige mit Melorheostose Léri. Dermat. Wchnschr [illegible] 1939

[illegible] [illegible] A P Ein Fall von Trophoedema chronicum [illegible] zur Menstruation, Zbl f Gynäk [illegible] 1927

varying with the sites within the central nervous system There occur sensory disturbances muscular atrophy beginning in the intermetacarpal muscles of the hands and ending up in characteristic contractions skeletal damage eye symptoms and spasms. The course of the disease is very slow the first symptoms usually remaining unrecognized over several years. The patients rarely die of syringomyelia but they often succumb to intercurrent infections.[194] Recovery hardly ever occurs.



Fig 350 —Nonne-Meige-Milroy disease Female aged 43 years Obesity mild pituitary symptoms, swelling of legs from childhood, became obese at puberty Mother had the same trouble. (Courtesy Wisconsin General Hospital)

Dermadromes —The dermadromes of syringomyelia are mainly due to the fundamental disturbance dissociated anesthesia. While the perception of pain and temperature become lost the sense of touch and deep sensibility remain undisturbed. Paresthesias are common in the early stages and the attempt to treat them with heat has often caused the first painless burns circulatory and possibly trophic influences may also play a part

[194] Bing R and Haymaker W Nervous Diseases, St Louis, 1939 The C V Mosby Co.

The patients hardly ever escape the traumatic and infectious complications. In advanced cases the hands are rarely found free of crusty sometimes rhagadi form ulcerations of varying sizes often located on the extensor surfaces of the fingers. Such trophic ulcers may lead to painless, destructive lesions around the nails. Mutilation resembling leprosy may ensue. These fairly characteristic finger affections are called panaris analgésiques. Transitory edema of the Quincke type[illegible] as well as lasting swellings represent another feature These swellings are often found on the hands giving them a succulent appear ance. The edema may disappear and leave a flaccid atrophic skin with a silky or papyraceous surface, or it may lead to a leathery uneven hypertrophy and hyperkeratosis unrelated to pressure or work (lizard skin) The appearance of unusual keratoses on the hands should make the physician think of syringomyelia. Regional[illegible] eruptions of large bullae in moderate numbers and unrelated to trauma may cause necrotic ulcerations[illegible] another parallel to leprosy

The nails may become affected in many ways. Hypertrophy and atrophy anomalies of position white color brittleness, groove formation and complete loss have often been described[illegible] The hair may gray early

The treatment is symptomatic. Protection from trauma especially burns is most important.

No skin manifestations were observed in 81 cases of amyotrophic lateral sclerosis[illegible] though symmetric pigmentations of the forearms had been de scribed earlier (Bowing after E. Kaufmann[illegible])

Diseases of the Brain

A variety of dermadromes may be seen as results of cerebral lesions.

Apoplexy may be followed by unilateral sweating of the paralyzed side (Binger and Berg after Marchionini[illegible]) This has been called 'hémiplégie sudorale' The galvanic skin reflex (Veraguth Tarchanoff's phenomenon) can not be elicited on the paralyzed side.[illegible]

Localized or unilateral swelling dryness, and in about half of the cases scaliness, occur Unilateral jaundice[illegible] occurs in *apoplexy* (See Chapter on Liver)

[illegible] Schirner O Hyperkeratosen der Handteller als Frühererscheinung bei Syringomyelie. Arch. f. Dermat Syph 173 27-33 1935

[illegible] Spillmann, L Présent les d'une malade atteint de gangrène cutanée d origine syringo-myélique Rev méd de l est 49: 290, 192 Zbl 21 80.

[illegible] Barney E. E. Syringomyelia Associated With Trophic Destructive Bullae Arch Dermat & Syph. 33 094-109 1936

[illegible] Frühwald Syringomyelie Zbl 48 287

[illegible] Wechsler J S Sapirstein, M R and Stein, A Primary and Symptomatic Amyotrophic Lateral Sclerosis (Cases) Am J M Sc 208 70-81 1944

[illegible] Essen, K W and Roberts H H Abh f des galvanischen Hautreflexes bei halbseitigen Hirnläsionen Deutsche Ztschr Nervenh 128 31-42, 1932

[illegible] Page I H Ipsilateral Edema and Contralateral Jaundice Associated With Hemiplegia and Cardiac Decompensation Am. J M Sc 177 373-378 1929.

Brain injuries may cause contralateral coating of the tongue,[2939,2940] alopecia[1072] and sudden unilateral graying of the hair and beard (Gowers after J.A.M.A.[2941])

Wartenberg[2942] observed isolated pruritus of the nose in *tumors* of the temporal lobe. He considered the itching and compulsory scratching of the nose, which persisted in deep sleep as a valuable temporal lobe symptom but other neurologists[2864] deny its localizing value.

Other occasional observations are unilateral seborrhea and sweating ecchymoses vitiligo and other pigmentary disorders of the skin[2944,2945] (See also neurocutaneous diseases)



Fig 360 – Unilateral edema of the face on paralyzed side. Three years after hemiplegia.

Urticaria factitia[2946] is supposedly pronounced in idiopathic *epilepsy* but not in the jacksonian type. During the epileptic fit the galvanic skin resistance is reduced.[2947]

The epileptic seizure may be preceded by vasomotor symptoms like blushing or pallor The acute spasms of the respiratory muscles and the concomitant increased pressure in the vena cava may cause petechiae

These are often found in the conjunctivae and in the skin of the neck, the chest and behind the ears.[2324] The petechiae are rarely numerous (ecchymotic mask)[2948] but they have some diagnostic or forensic value.[1943] Chloasma in the shape of the forehead ring occurs occasionally in epilepsy (See Encephalitis.)

[2939] Börnstein, W Trophische Veränderungen in der Zungenschleimhaut (herdgekreuzter Zungenbelag) bei corticalem Herd, Z Neur 104 776-790 1926

[2940] Levinger E U vollständiger Zungenbelag als vasomotorisch-trophisch Störung Deutsche med Wchnschr 52 I 707 708 1926.

[2941] Vitamins and Human Gray Hair Editorial, J A M A 122: 878-879 1943.

[2942] Wartenberg R Ein Schläfenlappensymptom, Arch. f. Psychiat 103 331 1935.

[2946] Camauër A. F Diagnostische Wichtigkeit des ödematösen oder urticariformen Dermographismus in der Neurologie, Acta. Conf lat Amer Neur etc. 1 96-110 1929 Zbl. 39: 185.

[2947] Porter J M J Galvanic Skin Phenomena in Epileptics, J Gen. Psychol. 11: 34-44, 1934.

[2948] De Blasi, A Sulla così det maschera ecchimotica, Ann ital di chir 13 493-510 1934

[2949] Millian, G Piqueté purpurique cervico-thoracique des crises comitiales, Rev franç. de dermat. et de vénéréol 4 137 138, 1928.

Traumatization of the central nervous system may cause *purpura* of a distribution which is apparently governed by the nervous system. Purpura up to the level of a spinal anesthesia,[illegible] or generalized symmetric purpura after skull fracture [illegible] pertain here.

Purpuric lesions have been described in many organic diseases of the central nervous system especially in multiple sclerosis.[illegible]

Diffuse *hypertrichosis* has been observed in encephalitis following *complicated fractures* [illegible] in glioma of the temporal lobe [illegible] in disseminated sclerosis,[illegible] and in several other lesions of the brain Hirsutism of this type may disappear with recovery

Encephalitis lethargica (Von Economo s disease) is an epidemic and contagious disease probably caused by a filterable virus. After an incubation period of approximately a week the disease breaks out with mild fever and influenza resembling symptoms often with icterus.

Meningitic symptoms are lacking or mild but ocular palsies and headache develop frequently

In the course of a week sleepiness or irritability increases. In the lethargic type the patient sleeps most of the daytime. He can be aroused only with difficulty At night he is often restless. In the irritable or hyperkinetic form the muscle tone is increased Tremor spastic paralysis, fever and delirium are the main symptoms. The acute stage may last several weeks or months. The mortality of the cases with a stormy onset may be as high as 33 per cent.

Another third of both types may recover completely and one third develops progressive or stationary sequelae among which Parkinsonism with paralysis agitans-like symptoms rigidity salivation tremor is the most common one (Von Economo after Bing and Haymaker[illegible])

In young individuals change of character hypomania and psychoses may follow The pathological characteristics are inflammatory infiltrations and hemorrhages in the gray matter of the large nuclei and the frontal lobes.

Dermadromes —Best known among a variety of skin manifestations of encephalitis lethargica is the profuse *seborrhea* [illegible] which has been found in from 35[illegible] to 48 per cent (Stern after E. Guttmann[illegible]) of the cases. Rattner[illegible] found unusual oiliness of the face in only 8 per cent This symptom has rarely been seen in true paralysis agitans.

[illegible] Ross, F Purpura nach Lumbalanästhesie. Klin. Wchnschr 1931 II 2341 2342.

[illegible] Kindler W Zur Frage der Purpura traumatica, München. med Wchnschr 75 823-824, 1928

[illegible] Schlaefer R. Nervensystem und postane Blutungen, Berlin, 1927 S. Karger

[illegible] Cuccisposti G B Sindromi encefalitiche con retropulsione catalessia ed ipertricosi, Cervello 10 13 20 1931

[illegible] Markoff K Hirsutism in Woman With Glioma of Left Lobe of Brain, Schweiz med Wchnschr 69 43-47 1939

[illegible] Levinger E Ueber Entwicklung von Hypertrichose bei [illegible] multipler Sklerose Z. Neur 122: 490-509 1929

[illegible] Cohn, T Encephalitis ohne Lethargie während der Grippeepidemie Zbl Neur 20 200, 1920.

[illegible] Weidman, F D Seborrheic Dermatitis in Post Epidemic Encephalitis Arch. Derm & Syph. 21 690, 1930.

[illegible] Rattner H. Changes in the Skin in Chronic Encephalitis, Arch Dermat. & Syph. 31: 26-37 1935

In typical cases the face appears as if it were covered with grease. If the grease is wiped off it reappears within about 20 minutes. Facial puffiness[1956] and complicating seborrheic dermatitis is not uncommon.[1957] Seborrhea is comparable to other disorders of secretion like hyperhidrosis and excessive salivation and lacrimation which may cause chronic blepharitis and dermatitis of the lids. The cause of the seborrhea is supposedly an inflammatory irritation of a center in the wall of the third ventricle.[1959] Perutz[1960] could produce seborrhea in rabbits by stimulation of the interbrain.

Trophic ulcers[1961] mostly in the nasolabial folds or around the nasal orifices sometimes invading the nasal septum and the upper lip have often been described.[1962] The lesions may be very destructive and hard to cure.



Fig 361



Fig 362

Figs 361 362.—Brow forehead ring in encephalitis lethargica. (Courtesy Prof. H Haxthausen, Copenhagen.)

These postencephalitic ulcers have in some instances been mistaken for rodent ulcers. The sensitivity of pain and touch is preserved. Analogous ulcerations in other areas e g the hands[1963] and the t ngue (Schurmer and

[1959]Stiefler G (a) Seborrhoea faciei als ein Symptom der Encephalitis lethargica, Z Neur 73 456, 1921 (b) Seborrhoea faciei als isoliert postencephalitische Veränderung Wien klin Wchnschr p 334, 1924

[1960]Perutz, A Lustig B and Klein, A E Zur zentralen Regulierung des Fettstoffwechsels der Hautoberfläche, Arch f Dermat Syph 170: 511-520, 934

[1961]Hoffman, H Large Trophic Ulceration of Nose and Mouth Following Lethargic Encephalitis (Parkinsonism) Deutsche med Wchnschr 52 238-239 1926

[1962]Rosenberg, S J and Solovay J Trophic Ulcer Following Encephalitis Lethargica, Arch. Dermat. & Syph 39 825-830 1939

[1963]Michon, P Troubles trophiques cutanés et parkinsoniens localisés, Bull Soc. franç de dermat et syph. 38 1093-1094 1931

Baumann after Marchionini[illegible]) are much rarer The localization in the naso-labial folds suggests a connection with the seborrhea which is most active in this site.

Chloasma[illegible] especially in the form of the brown forehead ring has been found repeatedly[illegible] Such chloasmatic pigmentations are also known to occur in other intracranial processes e.g epilepsy The typical brown forehead ring has the shape of a crossbow closely paralleling the hairline in the center and descending symmetrically toward both lateral ends of the eyebrows. A nonpigmented zone separates the hair as well as the eyebrows from the lesions.

Other reports on postencephalitic dermatoses include symmetrical gangrene[illegible] urticaria factitia, Quincke's edema,[illegible] multiple paronychias (Schirmer after Marchionini[illegible]) severe subungual hemorrhages[illegible] diffuse alopecia resulting in almost total baldness in 4 cases[illegible] bullous eruptions[illegible] and Herpes Zoster[illegible] in 16 cases.

[illegible] Harthausen, H. Skin Changes Following Encephalitis Lethargica, Acta dermat. venereol. 13 409-416 1932

[illegible] Anderson, O and Wernoe, T B Der braune Stirnring, Ugesk f laeger 1930 II 817-821 Zbl. 58: 214

[illegible] Büchler P Vasomotorisch trophische Störungen bei Encephalitis epidemica, Gyógyászat 61 718, 1923 Zbl. 32: 174.

[illegible] Von Poor F Hämatom des Nagelbettes bei postencephalitischem Parkinsonismus, Dermat. Wchnschr 1931 I 45

[illegible] Stiefler G Zur Klinik der Encephalitis lethargica, Wien. klin. Wchnschr 33 [illegible] 1920

[illegible] Vetter A 16 observations d zonas dans l encéphalite léthargique Zbl. 36 313

Chapter XL

PSYCHOSES AND PSYCHODERMATOSES

Psychoses

Kretschmer's[2370] work on physique and character correlated schizophrenia and the schizothymic personality with the asthenic and athletic builds and the circular psychoses with the pyknic type. Though many of Kretschmer's "affinities" have been disputed[2371] the cutaneous dermadromes observed by him have to some extent been confirmed by his opponents.[2372] This is particularly true of the *hair growth* in the main types of psychoses. In the circular group a tendency toward hirsutism is striking. These patients frequently have marked lanugo and axillary and pubic hair. The men have a well developed beard growth of soft texture and equal distribution. The hair often seems lighter during the *stuporous period and becomes darker or reddish in the stage of excitation*. Such color changes were noticed as early as on the first day of the mental change.[2373] In a 21 year-old blonde woman the hair became partly white during several attacks of dementia praecox but it turned normal again when the spell ended.[2373]

Male baldness seems to be more common among the circular than in the schizophrenic group and there is a difference in the character of the baldness. The circular pyknic[2370] has pronounced temporo-frontal calvities. If he is bald the baldness is shiny and sharply bordered. Kretschmer calls it a "beautiful bald pate." The baldness of the schizophrenic is usually less complete, ill defined and irregular.

There is a tendency to formation of folds in the scalp. *Cutis verticis gyrata* and other acromegaloid traits, have been found in schizophrenes by several observers.[24, 2375] The head hair of the asthenic or athletic schizophrene is often coarse in comparison with the soft hair of the pyknic circular. On the forehead as well as on the nape of the neck the hairline is often straight and there is no temporo-frontal notch. Frequently it is lower so that a "*fur cap*" type of head hair results. Bridges of hair from the head to the eyebrows and down to the lanugo of the back have been frequently found.[2370] Junction of dense eyebrows (Synophris) occurs occasionally. The terminal hair of the male schizophrenic is relatively weak, though often coarse, while the female schizophrenic has a tendency toward

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[2370] Kretschmer, E.: Körperbau und Character, ed. 2, Berlin, 1922, Julius Springer.

[2371] Betz, B. J.: Somatology of the Schizophrenic Patient, Human Biol. 14: 192-234, 1942.

[2372] Kolle, K.: Körperbaustudien bei Psychosen. Die männlichen Zirkulären, Arch. f. Psychiat. 77: 115-150, 1926.

[2373] Eller, J. J.: Neurogenic and Psychogenic Disorders of Skin, M. J. & Rec. 129: 481, 554, 616, 1929.

[2374] Finkelstein, B. A.: Cutis verticis gyrata bei akromegaloiden Katatonen, Monatschr. f. Psychiat. Neurol. 105: 104-108, 1942.

[2375] Tomasino, A.: Rara anomalia del cuoio capelluto "rughe pliche" in un demen. precoce. Arch. di antropol. crim. 55: 1004-1013, 1935. Zbl. 54: 101.

hirsutism.[2376] The latter observation is in contrast to Kretschmer However there is a general impression that some degree of hirsutism is found relatively often in various psychoses.[2377, 2379]

Alopecia totalis may occur in connection with depression [2380] however the depression may also be of a reactive character due to the disfiguring loss of hair

Heller[2381] was unable to confirm earlier claims of unexplainable and characteristic *nail* changes in psychoses. It is an old belief that the insane have long or unusual nails but this is not true.* The transverse lines can usually



Fig. 261 Mental retardation. Fur cap hair line (Courtesy Wisconsin General Hospital.)

be traced to intercurrent disorders. Under proper care the nail of the inmates of asylums may be in better condition than the nails of the average population

Repeated loss of the nails and of the hair in circular psychosis has been described (Troisfontaines after Heller[2381])

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* The same hour was the thing fulfilled upon Nebuchadnezzar and he was driven from men, and did eat grass as oxen, and his body was wet with the dew of heaven, till his hairs were grown like eagles feathers and his nails like birds claws Daniel, IV 33.

[2376] Mumford P B and Chevens, L C F An Investigation in the Physical Characteristics of the Skin in Some Types of Psychosis, J Ment Sc 78: 242-252, 1932

[2377] Elliot H E Comparison of Non-psychotic Women With Schizophrenics With Respect Body Type Signs of Autonomic Imbalance and Menstrual History Psychiatric Quart 15 17-22, 1941.

[2378] Epstein, A. L Some Biological Studies in Psychiatry V II J Nerv 103 ...-..., 7.. 1933

[2379] Turpin, C J Daniel C and Cavaman, K Étude anatomoclinique sur ... cas de virilisme pilaire, Rev franç d endocrinol. 8 73-108, 1933 Ibid 13 497

[2380] Allen, C., and Carlyle-Gall, L. Depression-Hyponormal-Alopecia-Syndrome, Brit. M. J 2: 67-68, 1942.

The observations on the status of the skin in the insane have not yielded many tangible results Vascular symptoms are first on the list Kretschmer[illegible] also Mumford and Chevens[illegible] emphasize the rosy complexion of the circular pyknic in comparison with the pale asthenic schizophrenes.

The *vasomotor* lability of the pyknic also expresses itself in a greater tendency to blushing and rosacea. Some authors found the skin of the circular in good condition rather moist with a well developed panniculus adiposus. The skin of the schizophrene is usually paler flaccid and unhealthy Acne is frequent.[illegible] Dryness and a *keratotic* tendency has often been considered a characteristic of the skin of the insane[illegible] Mumford and Chevens[illegible] relate this symptom to the schizophrenic.



Fig 344—Mental debility Female aged 42 years. Hypertrichosis

The most important vascular phenomenon of the schizophrene is *acrocyanosis* This has been confirmed by many writers.[illegible] Closely related to the acrocyanotic syndrome is the pseudo-edema of the insane (Dide Trepsat Kraepelin after Simon[illegible]) In acrocyanosis the acra are bluish with red vascular patterns cold slightly swollen but not pitting The swelling may reach up to the knees and a fold may be marked at the ankles and at the base of the toes. There is prolonged white dermographism with red borders, lasting from one and a half to two hours.

Red dermographism is common in a great variety of psychoses.[illegible]

Generalized addisonoid *melanoderma* in catatonic schizophrenia has been observed in several instances[illegible]

Spontaneous and unexplained bullae with subsequent ulcerations, occur even in bedridden patients without undue exposure to traumatism. In the *mentally deficient* anomalies of the hair pigmentation acrocyanosis, pseudo-

[illegible] Goldbladt H and Dermann [illegible] Sur la sécheresse de la peau chez les aliénés, Schweiz Arch f Neurol & Psychiat 19 234-241 [illegible]

[illegible] Stern, E S Etiology and Pathology of Acrocyanosis, Brit J Dermat & Syph. 49: 100-108, 1937

[illegible] Simon, C Dermatoses en rapport avec des troubles du système nerveux Nouvelle pratique dermatologique vol 8 Paris 1936, Masson & Cie pp 749-[illegible]

[illegible] Petroselli F Il dermografismo nelle psicopatiche Cervello 11 40-46, 1932 Zbl. [illegible]

[illegible] Wigert V Katatonie und Melanodermie, Acta psychiat. (Kopenhagen) 1 [illegible]-144 [illegible]; Zbl. [illegible] 218.

edema malformations nevi hemihypertrophy[illegible] and scars from biting the hands and wrists[illegible] have frequently been recorded but the statistics are controversial and[illegible] some lack sufficient controls. Mumford and Chevens[illegible] emphasize the juvenile character of the skin in mentally retarded adults.

The dryness of the skin and hair the tendency to eczematous eruptions the large protruding tongue malformations of the ears, epicanthus and mongol spots[illegible] are the well known external signs of *mongoloid idiotism* Familial xeroderma pigmentosum may be associated with severe retardation [illegible]

Psychogenic Dermatoses

A great number of *cutaneous reactions to psychic stimuli* are known One has to assume that the autonomic system mediates the psychic impulses to the effector organs in the skin by the liberation of acetylcholin or sympathin (See autonomic system) Pallor blushing perspiration gooseflesh and the graying of the hair are proverbial phenomena caused by fear shame rage embarrassment excitement, worry and other psychic factors. Certain sensations in the skin like spine tingling shuddering itching and hair raising may also be produced by merely psychic causes, e.g reading an exciting story fear acoustic stimuli as sour notes and shrill sounds or the touching of certain materials like silk cardboard and rough wood Using laboratory methods very sensitive responses can be demonstrated. Not only actual sensations but even the mere imagination of a sensation like pain reduces the electric resistance of the skin in a typical way which is demonstrable by Tarchanoff's psycho-galvanic reflex This accurately measurable drop in electrical resistance is due to the sympathetic stimulation of the sweat glands.[illegible]

The skin temperature depends on the arterial tonus which responds readily to psychic stimuli A local temperature increase of 0 2 centigrade can be caused by mental concentration on a spot [illegible] The famous lie-detector is based on such psychogenic reactions in the skin and other organs. It is not difficult to conceive that inflammatory processes, which are so intimately related to vasodilation may in some instances be produced by psychic causes. Many experiments have proved the truth of this assumption There are many clinical observations which support the *psychogenic* etiology *of some dermatoses* but it is more often true that psychic stimuli enhance or impair an existing dermatosis than that they actually cause it The experimental methods do not try to explain the psychic part of the sequence emotion—somatic changes. They concentrate on the latter part The greatest attempt not to explain or to locate the psyche

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[illegible] Wakefield E G Congenital Hypertrophy of Left Shoulder Girdle Arm, and Hand With Nevus and Varicose Veins Am J M Sc 171 869-874, 1926.

[illegible] Butterworth Th and Wilson, M J Incidence of Diseases of the Skin in Feebleminded Persons Arch Dermat & Syph 38 203-209 193[illegible]

[illegible] Clark N H M Stigmata of Degeneration in Relation to Mental Deficiency Proc. Roy Soc. Med 24 413-425 1931

[illegible] Brushfield T Mongolism Brit J Child Dis 21 241-258 1924

[illegible] De Sanctis C and Cacchione A L'idiozia xerodermica, Riv sper di freniat 56 269-292 1932 [illegible]

[illegible] Berger H Psychische Beeinflussung der Hauttemperatur Journ. f. Psychol. Neurol. 27 209-221 1922

but to permit a glimpse of its mechanisms has been made by Freud and his psychoanalytic school

According to this doctrine the powerful source of psychic energy the mystic Id makes contact with somatic processes somewhere in the form of instincts. A resistance is set up against the demands of the instincts (Freud after Hinsie and Shatzky[illegible]) This leads to conflicts because the suppressed or repressed instincts are not deprived of their power They continue to seek discharge comparable to potential energy which tends to transform itself into kinetic energy Somatic processes including disease may be one of the forms of transformation In this way conflicts may lead to disease The term psychodermatosis seems appropriate for dermatoses of psychogenic origin

The case material illustrating the psychogenesis of dermatoses is large but not always conclusive Small numbers the fluctuating course of the dermatosis in question and accompanying dermatological treatment often obscure the evidence which is supposed to prove psychogenesis But in spite of these limitations the existence of psychogenous dermatoses and the value of psychotherapy cannot be denied [illegible]

Vascular Phenomena—Psychogenic *erythema* as an expression of modesty embarrassment or excitement is usually restricted to the face and neck. About the neck or upper chest it may assume a blotchy pattern especially in women who generally are much more likely to blush than men Children of both sexes seem to blush equally with various emotions especially with guilt on telling a lie Emotional erythema has been seen in atypical sites to which the mind of the patient had been concentrated A patient blushed emotionally around a tuberculous sinus of long standing [illegible] A woman who is examined gynecologically for the first time may show emotional erythema on her abdomen [illegible]

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*The word neurodermatosis should be restricted to the dermadromes of organic diseases of the nervous system The word neurose is often being used for relatively minor disorder of the psychic constitution which is not psychosis

[illegible] Hinsie L E and Shatzky J Psychiatric Dictionary New York, 1940 Oxford University Press

[illegible] Beck, W T Psyche and Haut, Handb d H Gk 4, 2 1302-1402, 1933.

[illegible] Gillespie, R. D Psychological Aspects of Skin Diseases, Brit. J Dermat 50 1 16 1938

[illegible] Mayr J K Ueber Psychogenese von Hautkrankheiten, Zbl 23 1 32.

[illegible] Klauder J V Psychogenic Aspects of Diseases of the Skin, Arch Dermat. & Syph. 33 221 233 1934.

[illegible] MacKee G M Neurotic Excoriations, Arch Dermat & Syph 1 256, 1920

[illegible] Wertber J Die neurotischen und hysterischen Dermatosen, Dermat Wchnschr 1933 I 461-470, 513-518.

[illegible] Pusey W A and Senear F E Excoriations Cases, Arch Dermat & Syph 1 270 1920.

[illegible] Michelson, H E The Motivation of Self-Induced Eruptions Arch Dermat. & Syph. 51 245-250, 1945.

[illegible] Obermayer M E Functional Factors in Common Dermatoses, J A M A 122 863, 1943.

[illegible] Lynch, F W Hinckley R G and Cowan, D W Psychobiologic Studies of Patients With Atopic Eczema, Arch. Dermat & Syph. 51 251-260, 1945.

[illegible] van de Erve, J M and Becker S W Functional Studies in Patients With Neurodermatoses. J.A.M.A. 105 1093, 1935.

Blushing and fear of embarrassing blushing can sometimes be traced to early sexual emotions. The psychoanalysts found an underlying Oedipus complex in some pronounced cases.[illegible]

Psychogenic *hemorrhages* may be caused by a gruesome sight [illegible] or similar experiences. Schindler [illegible] who has devoted a monograph to the subject of spontaneous neurogenic and psychogenic hemorrhages, saw the purpuric spots most often on the lower legs of hysterical persons.

He describes three cases which were cured by hypnosis or psychotherapy. The purpuric lesions could be provoked by hypnotic suggestion [illegible] Kohnstamm could inhibit bleeding from needle pricks by the hypnotic suggestion that the pricked left index finger would not bleed. The pricked index finger of the right hand for which normal conditions had been suggested bled in the usual manner [illegible]

Mystic Stigmatization —In this connection the phenomenon of *stigmatization* has to be mentioned. The term is derived from the sixth chapter of the Epistle to the Galatians in which the Apostle Paulus says I wear the mark (stigmata) of the wounds of Jesus on my body [illegible] Thus it means the appearance of skin lesions resembling the wounds suffered by Jesus during the crucifixion

The numbers of more or less well acknowledged cases vary from 80 to 321 according to various Catholic sources.[illegible] The Catholic church has, at least in modern times, exercised great skepticism in this matter The most famous and if Saint Paul s word is not taken literally probably the first of the stigmatized was Saint Francis. Sixty two have been beatified or canonized. A medical report of an eighteenth century case of stigmatization including autopsy has recently been made accessible [illegible] Twenty-nine cases occurred in the nineteenth century and at least three have been observed by trained modern scientists. The last case was that of the still living Theresa Neumann of Konnersreuth in the Bavarian Palatinate The case probably resembled earlier observations in many respects.[illegible] Ewald [illegible] professor of psychiatry at the University of Erlangen who observed Theresa and furnished a now famous expert opinion for the physician of the bishop of Regensburg saw nickel-sized dry scab covered hemorrhagic and tender lesions on the dorsa of the hands and feet The scabs developed from blood which oozed through the thin epidermal membrane during the ecstasies. There were smaller lesions on the corresponding spots of the palms and soles, and over the heart next to the sternum. The latter the so-called chest wound had a slightly raised edematous appearance.

[illegible]Werther, J A Symposium on Psychogenic Dermatoses, Dermat. Wchnschr 94 20, 1932

[illegible]Jakobi, W Die Stigmatisierten. Beiträge zur Psychologie der Mystik. Grenzfragen d. Nerven- u Seelenlebens, No. 11 pp 1-57 München, 1923, J F Bergmann.

[illegible]Schultz, J H Stigmatisation, Deutsche med. Wchnschr 53 1064-1066, 1927

[illegible]Simon, O Les Stigmates cutanées des mystiques, Bull méd Paris 47 667-671 1933.

[illegible]Ewald, G Die Stigmatisierte von Konnersreuth, Untersuchungsbericht und gutachtliche Stellungnahme, München med. Wchnschr 74 1981 1982, 1927

The American dermatologist Klauder[1909] who examined Theresa nine years after Ewald[1908] found a remarkably square dry glazed hemorrhagic lesion without any inflammation ulceration or destruction The clot seemed in the skin rather than on it Klauder[1909] also saw sharply outlined pear shaped, con gestive areas 0 5 cm. long on the forehead. These stigmata which symbolized the wounds from the crown of thorns, did not have crusts.



Fig 365 — St Francis receiving the stigmata (Painting by Francisco de Zurbaran. With permission of the Musée d Louvre, Paris)

On Friday Theresa went into a state of ecstasy in which she seemed to en dure or witness the crucifixion of Christ During her ecstasy the stigmata be- came redder The marks did not heal in the interval In the scant secretion of the thoracic stigma and in the tears blood was found microscopically Accord ing to reports which Ewald could not verify and the objective truth of which he could not believe Theresa did not eat more than a quarter host with 3 c.c. of water daily There were no stools but small quantities of urine containing

[1909] Klauder J V Stigmatization, Arch. Dermat & Syph. 37 650-659 1938.

acetone, were secreted The girl lost nine pounds during the ecstasy but regained her weight during the interval in spite of doing house work and other activities. Ewald and other medical observers[illegible] arrived at the opinion that Theresa's stigmata were genuine, and not artificially produced

The psychiatric diagnosis made not only from the ecstasies but from many other preceding manifestations, was severe hysteria.

Allergic Phenomena —Purely psychogenic *urticaria* is rare[illegible] Psychic factors however were noticeable in 18 per cent of 170 cases[illegible] of urticaria and angioneurotic edema. Stokes Kulchar and Pillsbury[illegible] in a thorough study of 100 cases, estimate that psychogenous influences are the sole cause of urticaria in 12 per cent and a contributory cause in 68 per cent The urticariogenic, psychogenous background seems to be in a personality type rather than in external impinging circumstances[illegible] Allergic urticaria may result in a conditioned reflex and persist long after the exposure to the excitement has ceased.[illegible] Hebra described the case of a woman who developed urticaria by the mere thought of some urticariogenic substances (Veidsen in discussion to Kohnstamm and Pinner[illegible])

In a well observed case[illegible] of suspected allergy to quinine urticaria could be produced by hypnotic suggestion of taking quinine, and quinine could be taken in hypnosis without producing urticaria if it was suggested that it was not quinine. Kohnstamm[illegible] performed the following experiment in the presence of a group of neurologists. A cross was drawn with a pencil on both arms of a subject under hypnosis. The suggestion was given that on the left side an urticarial wheal would develop within two hours whereas the right side would remain unaltered After about an hour under supervision the wheal formation on the left side began Urticaria factitia was excluded

Some patients develop urticaria on excitement. Some are able to produce wheals in a certain spot by mental concentration on this area.[illegible] Urticaria after coitus probably belongs to this group.[illegible] Dermographism is supposed to be common in neurotic patients.[illegible] The cholinergic character of emotional urticaria has been thoroughly investigated. Rothman[illegible] considers this condition

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[illegible] Drake, J A. Urticaria Evoked by Emotion, Brit J Dermat 43 184-188 1931

[illegible] Dunbar H. F Physical and Mental Relationship in Illness, Am. J Psychiat. 91: 541-562, 1934.

[illegible] Jarcho, S. Kambercard Life of Maria Caterina Brendl, Bull Hist Med 16 403-419 1944.

[illegible] Fink, A. I and Gay L. N Review of 70 Cases of Urticaria and Angioneurotic Edema, J Allergy 5: 615, 1934 also Bull Johns Hopkins Hosp. 55 280-303, 1934

[illegible] Stokes, J H Kulchar G V and Pillsbury D M Effect on the Skin of Emotional and Nervous States. (Urticaria) Arch Dermat & Syph. 31 470-499 1935.

[illegible] Stokes, J H. The Personality Factor in Psychoneurogenous Reactions of the Skin, Arch. Dermat & Syph. 42: 780-801 1940.

[illegible] Bierman, W Treatment in Peripheral Vascular Disease, Arch Phys Therapy 21 367 [illegible] 1940.

[illegible] Sack W Zum Mechanismus der psychophysischen Schaltung, Nervenarzt 6 57-62, 1933.

[illegible] Kohnstamm, O and Pinner M Quaddelbildung durch hypnotische Suggestion, Arch. f. Dermat. u. Syph. 91 370-380 1908

[illegible] Kartamischew A J Ueber d. Wesen der psychischen Urticaria, Arch. f. Dermat. u. Syph. 173 431-436, 1936

[illegible] Kohnstamm, O Demonstration Deutsche Ztschr f. Nervenh 43 447-448, 1911 1912.

[illegible] Hirschfeld, M Sexualpathologie, vol. 1 Bonn, 1922, A Marcus and E. Weber p. 84.

[illegible] Wengraf F Eine Dermatose post coitum, Psychother Prax. 1 80-82, 1934.

as one of the rare cases of allergy to a physiological metabolic product namely acetylcholin Rothman[illegible] has in two out of three cases successfully desensitized patients with emotional urticaria by gradually increasing intradermal doses of acetylcholin.

Many allergic phenomena like urticaria asthma and hay fever are highly subject to psychic influence There is much evidence accumulated that certain types of character namely the driving high-strung subtle intelligent, ambitious sensitive also the imbalanced and maladjusted predispose to allergy[illegible] Worry grief anxiety fatigue stress and strains, unsatisfied longing for love and affection may increase specific allergic reactions and prevent their healing[illegible] Experimental allergic wheals in persons with pronounced allergy can be increased or inhibited by hypnotic suggestions[illegible]

Other Psychogenic Dermadromes—*Sweating*—Mental stimuli, e.g mental efforts in solving an arithmetical problem pain or excitement, may in some persons evoke sudden frontal axillary and especially palmar sweating[illegible] Apprehension of having a wet hand when shaking hands may cause palmar perspiration

The sweat secretion generally but especially that of the palms and soles is a sensitive somatic receptor of psychic stimuli.[illegible] This is best demonstrated by Tarchanoff's psychogalvanic reflex (see above) which indicates increased perspiration by lowered electric resistance of the skin The shouting of words to the test person is sufficient to evoke the reflex. *Dyshidrosis* is in some cases quite subject to psychogenic factors.

Psychogenic blisters represent a more severe reaction than the changes which have been mentioned so far The blisters may even be followed by necrosis. While great skepticism prevails with regard to the so-called pemphigus hystericus of the older authors,[illegible] it cannot be doubted that bullae can be produced by hypnotic suggestion of a burn[illegible] Kreibich and Doswald[illegible] hypnotized a physician and touched him with a stick of wood suggesting that he was being burnt with a match After three minutes an erythema the size of a match head appeared and after three more minutes a blister of the same size was visible Biopsy after 24 hours revealed changes identical with that of a third degree burn[illegible]

Similar experiments have been repeated by many authors and with precautions which ought to rule out fakery including a plaster of Paris dressing during the experiment

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[illegible] Stokes, J H and Beerman, H. Psychosomatic Correlations in Allergic Conditions Problems and Literature, Psychosom. Med 2: 438-458, 1940.

[illegible] Diehl, F and Heinichen, W Psychische Beeinflussung allergischer Reaktionen, München. med. Wchnschr 78 1008- 009 1931

[illegible] Marcus, H and Sahlgren, E Untersuchungen über die Einwirkung der hypnotischen Suggestion auf die Funktionen des vegetativen Systems Acta psychiat et neurol. [illegible]

[illegible] Kuno Y Physiology of Human Perspiration. London, 1934, J & A. Churchill Ltd.

[illegible] Kosaka, T Demonstration of Psychical Sweating by Means of Minor' Method, Jap J med. Sci Trans. III Biophysics 2: 2, 1931 [illegible]

[illegible] Cascella, P Ipoevolutismi infantilismi universali nelle insufficienze psichiche, Rassegna di studi psichiat. [illegible] 421-445, 1930

[illegible] Kreibich, K., and Doswald, D C Posthypnotische Hautphänomene, Monatsh. f. prakt. Dermat. 47: 634-640 1908.

Herpes simplex and especially herpes genitalis is subject to psychogenic influences, such as guilt and fear of venereal infection after extramatrimonial coitus.

Pruritus is highly susceptible to psychogenic influences.[illegible] Every dermatologist knows of patients with lichen ruber and lichen Vidal chronic eczema psoriasis and prurigo whose skin disease is more itchy on excitement and calms down when the patient does However while mental impulses are very common contributory factors purely psychogenic pruritus is rare [illegible]

In order to prove the existence of completely psychogenic pruritus, Sack induced pruritus by hypnotic suggestion in the locally anesthetized finger of a patient. Pruritus may be a symptom in endogenous and reactive depressions.

The sexual background of anal and vulvar pruritus has frequently been analyzed [illegible] Many psychoanalysts believe that the pruritic seizures and the relief of tension achieved by violent scratching are sexual or homosexual equivalents. These relations seem to have been overemphasized.[illegible]

Psychogenic eczema is illustrated by the following case.[illegible] Psychoanalysis traced the origin of an eczema on the buttocks to a nauseating dream in which the patient had seen himself covered with feces as high as the eczema indicated Psychoanalysis cured the patient [illegible]

Sudden *blanching of the hair* caused by terrifying experiences is still controversial The two leading American textbooks of dermatology arrive at opposite opinions. Ormsby and Montgomery[illegible] admit it as a rare probability of clinical experience while Sutton and Sutton[illegible] explain it as the result of the removal of cosmetic coloration or of the application of a bleach The main argument against it is the lack of greater numbers of observation in both World Wars with millions of terrifying occasions. The number of well documented cases[illegible] seems too small to rule out the possible errors, especially that of having been gray before the event [illegible] The physiological possibility of a sudden graying must be admitted Landois's old theory that in such cases the pigment is hidden by reflecting gas bubbles has found considerable supporting evidence [illegible]

Mental stress, strain and shock, probably play an important role as a trigger factor in *alopecia areata*.[illegible]

In the opinion of the *psychoanalysts* psychogenic dermatoses always have a meaning [illegible] In some instances they symbolize their origin as in the case of ecchymoses after seeing blood [illegible] in the mystic stigmas, or in the cases of psoriasis provoked by the terrifying and prolonged sight of decomposing corpses in

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[illegible] Pearson, G. H. J. Some Psychological Aspects of Inflammatory Skin Lesions, Psychosomat. Med. 2: 22-33, 1940.

[illegible] Klauder, J. V. Psychogenic Aspects of Skin Diseases, J. Nerv. Dis. 84: 249-273, 1936.

[illegible] Bretschneider, A. Psychogene (oneirogene) Krankheitsbilder, Arch. f. Kinderh. 99: 81-85, 1933.

[illegible] Rogerson, C. H. Psychological Factors in Skin Diseases, Practitioner 142: 17-35, 1939.

[illegible] Vignolo-Lutati, C. Canicie precoce psicopatie di guerra, Policlinico (sez. prat.) 25: 460, 1918.

[illegible] Ingram, J. T. Baldness, Causes and Treatment, M. Press 207: 41-44, 1942.

[illegible] Schilder, P. Psychophysiology of the Skin, Arch. Dermat. & Syph. 20: 812-818, 1931.

front of trenches where the patient fought.[1937,1938] In some of these cases cure has been accomplished by hypnotic suggestion. Schilder[illegible] expresses the opinion without proving it that anal itching is an expression of sadomasochistic tendencies, blushing manifests a narcistic attitude and blisters and hemorrhages are closely related to a hysteriform attitude with a strong infantile Oedipus complex.

While classic psychoanalysis has found but little acclaim among the dermatologists, the importance of tensions, conflicts, emotions, overwork, fatigue, shock, worries, insomnia, inferiorities, frustrations, and other psychic factors on the origin and course of dermatoses has been emphasized time and again.

This has been done in the most human, practical and convincing way by Stokes.[1939] Purely psychogenic dermatoses are rare and do not develop typical morphological pictures with the exception of the self inflicted dermatoses.

Yet it is exceedingly common that the psyche influences the course of a disease for better or worse: psoriasis, lichen planus,[1940] chronic eczema, lichen Vidal, dermatitis herpetiformis and alopecia areata furnish the best examples (see also Obermeyer[illegible]). The psychosomatic relationship of *atopic dermatitis* is particularly striking.[1941] These patients are often highly intelligent, aggressive and ambitious, as well as tense and fidgety. It is more likely that their nervousness is primary rather than due to their itching and disfigurement which of course may also leave its mark. Their behaviour and character are quite different from other suffering or disfigured people. Family conflicts are often in the background of such cases, not infrequently caused by arguments on the treatment or diet. This was strikingly illustrated in one of the author's cases. An intelligent boy of 13 with severe atopic eczema improved immediately after the mother was advised to discontinue all discussions and arguments on his diet which had disturbed almost every meal. Later the trouble recurred on other conflicts. Overattention as an only child, or resentment because of sibling rivalry, frustration and parental rejection may also occasionally express themselves in more intensive itching and scratching and consequent impairment. The children soon learn to use their ailment as a weapon.[47,1941]

In this group probably belongs *acne urticata*.[1942] In this condition the lesions, which may occur on the face or anywhere on the body, are at first wheals or papules which itch intensely and become infiltrated and excoriated under constant scratching. They disappear after several weeks leaving a pigmented spot. The eruptions may keep appearing for years. In some of these cases a psychogenic background is obvious. In one of the author's cases the disease broke out in a young woman after the husband had gone overseas and eased up on the news

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[1937] Bunnemann, O. Psychogenese von Hautsymptomen, Ztschr. f. d. ges. Neurol. u. Psychiat. 88: 588-606, 193[illegible].

[1938] Bunnemann, O. Ueber psychogene Hautveränderungen, Psychotherapeut. Prax. 1: 33-38, 1934.

[1939] Stokes, J. H. Functional Neuroses as Complications of Organic Disease: A Office Technic Approach, With Specific Reference to the Neurodermatoses, J. A. M. A. 105: 1007-1012, 1935.

[1940] Goeckerman, W. H. The Relationship of Emotions and Cutaneous Lesions, Med. Clin. North America 14: 643-649, 1930.

[1941] Rogerson, C. H. Psychotherapy and the Asthma-Eczema—Prurigo Complex in Children, Brit. J. Dermat. 46: 368-378, 1934.

[1942] Kapoor, M. Ueber einige ungewöhnliche Formen von Acne (Folliculitis), Arch. f. Dermat. u. Syph. 201: 87-96, 1904.

that he was out of the danger zone. The patient was an intelligent high-strung person of a type commonly encountered in atopic dermatitis to which the condition seems to be related. Acne urticata also may be seen in atopic dermatitis.

Burning tongue is highly susceptible to psychic influence. In this condition the impulse may act through the sensitive psychosomatic mechanism of the gastric acidity Becker and Obermayer[1000] call *neuronychia* nail changes which either consist of separation of the nail from the bed or of superficial pitting thickening thinning or splitting The authors saw the condition associated with neurodermatitis or as the only somatic manifestation of nervous instability and exhaustion

Hysteria —Conscious or subconscious production of symptoms, the main feature of hysteria, leads into the field of the self-inflicted dermatoses (neurotic excoriations, dermatitis factitia) The variations of clinical appearance are innumerable but there are some features which are often encountered. The feigned



Fig 306.—Acne excoriée The scalloping is caused by ultraviolet light.

lesions are usually within the reach of hands, preferably of the right hand. The artefacts and their scars often have a strange angular round or linear "unnatural" appearance which arouses the suspicion of the experienced dermatologist[1044] Sometimes traces of a chemical used in the production of lesions *can be found in the surroundings or on the scab. If the* circumstances permit the application of a sealed occlusive dressing especially with plaster of Paris is advisable If healing of the suspected lesions of long standing follows, further evidence of self infliction is given

[1000]Becker S W and Obermayer M E Modern Dermatology and Syphilology Philadelphia, 1940, J B Lippincott Co

[1044]Gessner F E and Shelley H Neurotic Excoriations, Arch. Dermat. & Syph. 46 516-522, 1942.

However one should keep in mind that the typical pathomimic changes represent only a minority among the great variety of entirely or partially self inflicted lesions. More commonly a spontaneous dermatosis like acne or a patch of eczema is kept going by picking scratching or treating Excoriated acne is found not only in young girls (Brocq s acné excorié des jeunes filles) but also in middle aged women

The psychology of self induced eruptions[illegible] ranges from the sometimes criminal but simple and mentally normal cases of military or civilian malingering to more complicated and often decidedly pathological states of mind. *In one of these cases (Dieulafoy after Simon[illegible]) recurrent deep ulcera* tions of the hands and arms led to various major operations and finally to the amputation of one arm. The patient would not have hesitated to have his other arm amputated if the right diagnosis had not been made Under some grilling the patient admitted that he had placed pieces of potassium hydroxide on the



Fig 367 Trichotillomania.

mantlepiece and then put his arm on it Similar cases are on record. The most plausible motivation is an escape into disease The suffering arouses sympathy and attention which the patient is craving Strangely enough the motivation may also be lack of erotic attention A woman may try to get the sympathy and with it the love of her husband. This might be called the poor little dear motivation. Psychoanalysis may also detect underlying unconscious motives



Fig. 368.—Trichotillomania.



Fig. 369.—Trichotillomania. (Courtesy Division of Dermatology Department of Medicine University of Chicago.)

of guilt and punishment [2956,2958] In this group belong the patients who keep pyodermic lesions on the face open with tweezers.

Some of these patients are *feebleminded* who without any purpose follow an exaggerated urge to remove all little follicular plugs, to dig after or pull out ingrown hairs and to scratch every scale on the scalp.

The cases of neurotic excoriations lead to the true cutaneous *manias and phobias* There is the urge to rub the hair between the fingers, to bite the nails to break hairs or to pull the hair out (trichotillomania) This latter condition



Fig 270.—Neurotic excoriations.

usually found in children is often combined with anomalies like enuresis and mental retardation[2959,2960] paranoia[2961] or postencephalitic state[2962] It has also been observed as a psychic epidemic in institutions (Haldin Davis in discussion to O Donovan[2963]) Transitory cases without apparent deeper significance are also known [2964] Apparently unique is a case of plucking the mustache.[2965]

[2958] Cassana, R Sull'importanza di fattori psichici in dermatologia (a proposito di autolesioni cutanee in isteriche) Boll d Soc. med -chir Pavia 44 115-162, 1930 Zbl. 36 361

[2959] Dohl, S Ueber Trichotillomanie Dermat Ztschr 60: 236-239, 1930.

[2960] Tarozzi, G L Su di un caso di Trichotillomania, Pediatria prat. 10: 393-407 1933.

[2961] Ohashi, K Ein Fall von Trichotillomanie, Jap J Dermat. 33: 70 1933 Zbl. 42: 613

[2962] Perazzoni-Satta, O Considerazioni cliniche su un caso di pseudotricotillomania, Dermosifilografo 6: 449-460, 1931

[2963] O Donovan, W J Infantile Trichotillomania, Proc Roy Soc Med 26 836-838, 1933

[2964] Bleyer A Hair Plucking, Am J Dis Child, 51 336-337 1936.

[2965] Photinos, P B. Aetiologie der Trichotillomanie Dermat. Ztschr 61 339-340, 1931.

Cutaneous phobias and *hypochondriac complaints* which appear suddenly should be reason to search for an underlying psychosis[illegible] or addiction to morphine or cocaine

Patients who persistently bring little follicular plugs scales, or woolen fibers wrapped in paper or kept in a box to convince the doctor that they have worms or insects in their skin that they feel them creeping clicking digging and that they have to crush them between their fingers, have delusions and belong to a psychiatrist [illegible] Such delusions of parasites or dermatozoa may occur in the toxic psychoses in dementia praecox, in involutional melancholia, and in paranoia and paranoid conditions. The prognosis is poor Only about 10 per cent of the reported 51 cases have been cured [illegible] A greater significance may be attached to the severe cases of patients who wash their hands excessively avoid touching a door handle and have constant fear of body odor or of being dirty or of blushing



Fig 371 —Neurotic nail biting.

Tattooing, while normally a badge of membership to certain groups (sailors) or just being a fad may also express psychopathological conditions[illegible] with an erotic homosexual or criminal background During the second World War the rejection rate for tattooed men was almost 50 per cent greater than for nontattooed men and 58 per cent of all rejections among tattooed men were on the basis of neuropsychiatric disability in contrast to only 38 per cent among the nontattooed [illegible] These military statistics are according to the authors,

[illegible] Graham-Little E Neurotic Excoriations, Proc Roy Soc Med 24 654, 1931

[illegible] Ekbom K A Präseniler Dermatozoenwahn Acta psychiat et neurol 13 227 230, 1938

[illegible] Wilson, J W and Miller H E Delusion of Parasitosis (Acarophobia) Arch Dermat & Syph 54 39-57 1946

[illegible] Wright O S Psychosomatic Aspects of Dermatoses, Clinics III 711 737 1944

[illegible] Dreesberg, W Psychologic Motives in Tattooing Arch Dermat & Syph 30: [illegible]-892, 1934.

[illegible] Parry A Tattoo New York 1933 Simon & Schuster Inc

[illegible] Lander J and Kohn H M Tattooing Among Selectees Psychiatric Significance) Am J Psychiat. 100: 326-337 1943

based on numbers large enough to be valid though exact absolute figures are not given. Among the men rejected for antisocial inclinations 68 per cent had multiple tattoos.

Psychotherapy of Dermatoses.—If a psychic factor causes or, as it more frequently happens, influences the course of a skin disease, the removal of this cause should be tried. The office technique approach [illegible] may be learned depending on the interest and aptitude of the dermatologist, but at the present stage of our training the aid of a trained psychiatrist should be sought [illegible] to the greater advantage of both parties.

Hypnosis has occasionally been successful in the treatment of psoriasis[1961] and eczema.[1962]

The *psychotherapy of juvenile as well as ordinary warts* has been practiced by lay healers for centuries under many forms.[1963] Bloch[1964] stimulated scientific interest in the matter by healing 44 per cent of verrucae vulgares and 88 per cent of verrucae planae by verbal suggestion, painting with color, and turning on a buzzing electric motor. No consensus exists about the post hoc ergo propter hoc, but it is the impression of many experienced dermatologists that suggestion therapy is effective in a varying percentage. Some cases are very impressive.[1963,1965] Memmesheimer and Eisenlohr[1966] treated 70 out of 140 cases of ordinary warts by suggestion and left the other 70 untreated. There was no significant difference in the percentage of cures. The cure of condylomata acuminata by suggestion has been reported by Bonjour.[1967]

[1960] Weiss, E., and English, O. S.: Psychosomatic Medicine. Philadelphia, 1943, W. B. Saunders Co.

[1961] Wiech, J. M.: Anwendung der Hypnose bei Psoriasis, Dermat. Wchnschr. 100: 231-236, 1935.

[1962] Dubnikov, E.: Zur Frage der Behandlung des Ekzems nervösen Ursprunges durch Hypnotherapie, Vrach. delo 18: 634-636, 1935; Zbl. 48: 470.

[1963] Zwick, K. G.: Hygiogenesis of Warts Disappearing Without Topical Medication, Arch. Dermat. & Syph. 25: 508-521, 1932.

[1964] Bloch, B.: Ueber die Heilung der Warzen durch Suggestion, Klin. Wchnschr. 6: 2271-2275, 1927.

[1965] Dohi, S.: Heilung der Warzen durch Suggestion, Jap. J. Dermat. 30: 88, 1930; Zbl. 36: 318.

[1966] Memmesheimer, A. M., and Eisenlohr, E.: Suggestivbehandlung der Warzen, Dermat. Ztschr. 62: 63-66, 1931.

[1967] Bonjour, J.: La guérison des condylomes par la suggestion, Presse méd. 36: 61-67, 1928.

CHAPTER XLI

DISORDERS OF THE GASTROINTESTINAL TRACT

The various sections of the gastrointestinal tract are highly interdependent. Gastric hyperacidity for example may lead to increased motility of the small intestine causing the chyme to be rushed to the colon before the digestion in the bowel is completed. Thus toxic intermediate products may be reabsorbed and transported through the portal system to the liver where detoxification may take place provided the liver functions are unimpaired. A fraction however may enter the circulation directly through the vena cava. Deficiency of the antiseptic hydrochloric acid results in incomplete digestion and partial retention of the food. Another important consequence is the change of the intestinal bacterial flora, with ensuing putrefaction of large amounts of mucus. Local inflammatory lesions may change the permeability of the mucous membranes, thus permitting the passage of toxic and allergenic substances[illegible] through the intestinal barrier though much work remains to be done to *prove* the pathogenesis of skin changes by pathological absorption.

Dermadromes.—Yet cutaneous symptoms arise only in a small fraction of gastrointestinal disorders. No obligatory dermadrome is known in connection with gastrointestinal diseases but several dermatoses occur occasionally. The percentage of skin diseases in large series of gastrointestinal cases is small. Even the conditions commonly ascribed to gastrointestinal causes, such as pruritus, urticaria and eczema were recorded in less than one per cent of 5000 different gastrointestinal cases.[illegible] Among 595 gastrointestinal cases[illegible] rosacea was observed in 3.5 per cent.[illegible] In some groups, e.g. peptic ulcer or colitis, the incidence of dermatoses is higher. The percentages of varied gastrointestinal disorders in patients suffering from chronic eczema, neurodermatitis, urticaria, pruritus, acne, rosacea and acne urticata are significant. The possibility of a gastrointestinal cause should be kept in mind in persistent and unexplained cases of these dermatoses.

Mouth.—While the oral cavity is very often concomitantly affected by dermatoses, or takes part in manifestations of internal disorders, a primary mouth disease only rarely causes dermadromes. In this connection one should remember the role the teeth and tonsils play in focal infections. Perlèche may be caused by malocclusion and ill fitting or old dentures and salivation.[illegible]

[illegible] Urbach, E. Magen-Darmtrakt und Haut, Wien. med. Wchnschr. 1937 I 290-294, 323-326.

[illegible] Singer, O. Die endogene Natur mancher Hautkrankheiten, Verh. d. Ges. f. Verd.-u. Stoffwechselkr. Vienna, pp. 96-1 1 103-1[illegible], 1930 [illegible]

[illegible] Porges, O. Verdauungsstörungen und Dermatosen, Wien. klin. Wchnschr. [illegible] 1930.

[illegible] Bassler, A. The Entero-Dermal Syndrome. Urol. & Cutan. Rev. 35 504-509 1931.

[illegible] Beyn, A. Rosacea, Ibid. 62 402, 1934.

[illegible] Epstein, N. N. Gastric Analysis in Acne Rosacea, California & West. Med. 35 118-120, 1931.

[illegible] Freund, H. Perlèche bei Erwachsenen. Interlabialmykose und ihre symptomatische Bedeutung. Arch. f. Dermat. Syph. 164 [illegible] 1932.

The shape of the lips and the tendency to form persistent wrinkles or folds at the angles of the mouth may favor localized mycotic or bacterial infection particularly in diabetics. The author saw a mother of 75 years and her son of 52 years who both had a peculiarly hanging upper lip as a familial trait suffering from almost incurable perlèche. Persisting eczema of the face and cheilitis even severe papillomatous forms, may occasionally be caused by pyorrhea and oral ulcerations.[2975] Salivation especially during the night may well cause dermatitis which according to the sleeping habits of the patient may be unilateral[1140] or bilateral.

Diseases of the Stomach

A great number of investigators have tried to correlate the status of *gastric acidity* with skin disease (Spiethoff[2976] and later also investigations of his pupils Ehrmann[2977, 2978] Lejhanec after Ottenstein.) The results have shown that a general tendency to lowered gastric acidity exists in pruritus[2979] eczema neurodermatitis[2978] chronic urticaria rosacea[2979,2980,2981,2982] seborrheic



Fig. 272 — Chronic perlèche caused by ill-fitting dentures.

[2975] Dongen K van. Zusammenhang von Krankheiten im Munde und im übrigen Korper. Ztschr f Stomatol 32: 1109-1120 1934. Zbl 50: 102.

[2976] Spiethoff B. Magenstörungen bei Hautkrankheiten, München med. Wchnschr 60: 601-612.

[2977] Ehrmann, S. Ueber den Zusammenhang zwischen Verdauungsstörungen und Dermatosen, Wien klin Wchnschr 39: 756-757 1926.

[2978] Ehrmann, S. Ueber den Zusammenhang der Neurodermitis mit Erkrankungen des Verdauungstraktes und Störungen der inneren Sekretion, Arch f Dermat. Syph 155: 346-360 1928.

[2979] Urbach E. Rontgenologische und klinische Befunde am Magen-Darmtrakt bei Ekzemen und ihre Bedeutung für eine kausale Therapie, Arch f Dermat. Syph 162: 39-41 1930.

[2980] Eastwood, S R. Gastric Secretion and Other Digestive Factors in Rosacea, Brit J Dermat. 40: 91 104, 148-167 1928.

[2981] Stokes J H and Pillsbury D M. Dermatoses and Gastric Diseases, Arch Dermat & Syph. 22: 962-993, 1930.

[2982] Piper H G. Magensekretionsstörung und Haut, Dermat. Wchnschr 110: 317-323, 1940.

[2983] Brown, W H, Smith, M S and M Lachlan, A D. Fractional Gastric Analysis i Diseases of the Skin, 316 Cases Special Reference t Rosacea, Brit. J Dermat. 47: 181 190 1935.

dermatitis moniliasis in diabetes, kraurosis vulvae[illegible] and some other dermatoses.[illegible] Urbach[illegible] and also Ehrmann[illegible] emphasized the frequent (22 per cent) finding of hyperperistalsis along with anacidity in cases of neurodermatitis.

Great and almost unexplainable discrepancies exist among the many reports[illegible] (also Johansen after Ottenstein[illegible])

Newer investigations partly allowing for the physiological subacidity of the higher age classes,[illegible] have confirmed though not unanimously[illegible] that the gastric acidity tends to be subnormal in chronic inflammatory dermatoses[illegible] Lejhanec after Ottenstein) even if the involved skin area is relatively small [illegible]

The observations differ in the acute dermatoses and in the acute exacerbations of chronic skin diseases. Such states seem more likely to coincide with a tendency to hyperacidity This would be in line with observations of hyperacidity after mechanical irritation radiation with ultra violet light,[illegible] X-ray [illegible] skin irritations with mustard plaster[illegible] and extensive burns (Diehl Jr after Urbach[illegible]) Very severe burns however may cause anacidity (Geber after Urbach[illegible]) The serum of blisters from burns or freezing with CO^2 snow contains a histamine like substance.[illegible] It is therefore suggestive to explain the hyperacidity as the result of release of histamine from the inflamed skin [illegible] More difficult to explain is the subacidity in a relatively small lesion. In this case skin and stomach disorders are likely to be caused by a common factor The individual constitution also has a great influence on the acidity [illegible] The favorable effect of HCl therapy on some skin diseases would seem to prove that the subacidity is the cause of the skin disease Unfortunately the value of this often recommended treatment is not generally confirmed [illegible]

Elimination of toxic substances from the kin into the stomach may be the cause for gastric ulcers in extensive burns (Riehl J after U bach[illegible]) though thirty autopsy reports[illegible] do not mention such lesions. Little can be said as to whether ulcers associated with dermat tis[illegible] are due to eczema or

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[illegible] Gross, P Non-Pellagrous Eruptions Due Deficiency of Vitamin B Complex, Arch Dermat. & Syph 43 504-[illegible] 1941

[illegible] Ayres, S Jr Gastric Secretion in Psoriasis Eczema and Dermatitis Herpetiformis, Arch. Dermat. & Syph [illegible] 1929

[illegible] Waller S Beiträge zur Aetiologie der Ekzeme Orvosi hetil [illegible] 111 112, 1921 Zbl 2[illegible]

[illegible] Stokes, J H and Beerman H Effect on the Skin of Emotional and Nervous States. IV The Rosacea Complex Arch Dermat. & Syph [illegible] 478-491 1932

[illegible] Bergman, O Katarrhlehre von Ulcus pepticum und Hautkrankheiten, Wien klin Wchnschr 47: [illegible] 1934

[illegible] Vonn, H and Vonn. F Veränderungen der Magensekretion nicht als Ursache sondern als Folge von Hautkrankheiten. München med Wchnschr 1937 II 1 [illegible]

[illegible] Vonn, F Relation Between Disorders of Secretion and Skin, Dermat Wchnschr 111 [illegible] 1940.

[illegible] Diehl, F Die Wirkung der Ultra violet bestrahlung der Haut auf die Magensaftsekretion Naunyn-Schmiedeberg Arch 159: 367-371 [illegible]

[illegible] Antonio M Sulla modificazione della secrezione gastrica per effetto di stimolazione sull [illegible] della regione epigastrica. Arch ital d mal d app diger 1 [illegible], 1932 Zbl 42: 191

[illegible] Dumas, A and Anselme E Relations entre la peau et le [illegible] digestif Verh. 9 Internat Kongr Dermat 1 [illegible] 1935 Also 2: 22-36 1936 Zbl [illegible] 74 and [illegible]

[illegible] Colebrook L and others Studies of Burns and Scalds Medical Research Council [illegible] Report Series N 249 London, [illegible] His Majesty Stationery Office

[illegible] Lortat-Jacob, L Skin Diseases and Functional Disturbances of Various Organs Presse méd [illegible] 1699-1702, 1934

vice versa or whether ulcers and dermatoses have a common cause. The impression prevails that there exists a more than coincidental relationship

The advent of *gastroscopy* has recently revealed some relations which were not known before The gastric mucosa takes part in cutaneous lichen planus in about 20 per cent of the cases. Urticaria may show in the stomach and skin simultaneously [illegible] Vesicular gastritis has been seen to accompany some cases of acute vesicular dermatitis. In stationary eczema the gastric mucosa has usually been found in normal condition Gastritis of varying degrees of severity was present in 18 out of 19 patients with rosacea whereas among the 15 control cases of other dermatoses only 4 patients showed evidence of gastritis.[illegible] In 2 patients coincidental improvement of both gastritis and rosacea could be visualized by the gastroscope.

Urbach[illegible] suggests that the dysfunction of the gastric mucosa may lead to increased permeability for substances from incompletely digested food which normally cannot be absorbed This may cause allergization with cutaneous symptoms like urticaria eczema pruritus, urticaria, papulosa etc. Abnormal absorption of allergens may also occur from gastric or duodenal ulcers.

The validity of the old observations regarding the *tongue in gastric conditions* has recently been checked by Ostway and Middleton [illegible]

The surface of the tongue reflects the acidity of the stomach quite reliably In *hyperchlorhydria* and also in peptic ulcer the tongue is rarely smooth but often scrotal or coated Superficial defects may appear in the fur of the posterior tongue a lesion which has been related to gastric ulcer [illegible] In *achlorhydria* or subacidity smoothness of the tongue is common and still more so when achlorhydria is combined with anemia The patients often complain of soreness of the tongue and a dry throat though objective changes are frequently absent.

The Small Intestine

Pain distention audible peristaltic noises, nausea vomiting diarrhea and constipation are the primary symptoms which characterize disorders of the small bowel (Ingelfinger in Portis[illegible])

Besides the inspection of the stools chemical microscopic, bacteriological and helminthological examinations should be carried out Enteritis without any involvement of other parts of the tract is relatively rare.

Dermadromes —*Pruritus* [illegible] urticaria and eczema have been frequently found to accompany enteritis The connection was usually demonstrated by

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[illegible] Chevallier P and Moutier F L'estomac des eczémateux, Verh. 9. Internat. Kongr Dermat. 2: 107 112, 1936 Zbl 54 590

[illegible] Chevallier P and Moutier F L'estomac dans l'eczéma vulgaire à début et à prédilection antibrachiaux, Nutrition 6 19-31 1936 Zbl 54 593

[illegible] Urbach D Gastroscopic Observations in Rosacea, Arch. Dermat. & Syph. 44 251 255, 1941.

[illegible] Ostway W S J and Middleton W S. Correlation of Lingual Changes With Other Clinical Data, Arch. Int. Med 49 860-876 1932

[illegible] Glaessner K Ueber Ulcusnarbe, Arch. Verdauungskr 51 60-73 1932.

[illegible] Portis, S A. Diseases of the Digestive System, Philadelphia, 1944 Lea & Febiger

the effect of dietary measures[illegible] or intestinal treatment with activated charcoal[illegible] after protracted topical therapy alone had failed. Protein putrefaction and carbohydrate fermentation could frequently be demonstrated in the feces in eczema especially perianal eczema acne, urticaria, pruritus[illegible] and infantile eczema [illegible] The bacterial flora produces porphyrins, the light sensitizing property of which is well known

Urinary indoxyl a sign of intestinal putrefaction was not found increased in 42 cases of eczema [illegible] Vaccines derived from fecal bacteria have been found useful in the treatment of some dermatoses, but this method has not found much acclaim from dermatologists. Achylia gastrica and enteritis may be followed by the accumulation of feces and mucus in the cecum with subsequent inflammation This typical syndrome of *typhlitis* (cecitis)[illegible] with dull pain in the ileocecal region is often mistaken for appendicitis. Neurodermatitis lichen urticatus, urticaria and eczema have quite frequently been found associated with typhlitis. These dermatoses disappeared after treatment of the typhlitis with HCl and a diet free of irritating cellulose fibers.[illegible] Creosote has been advocated as an intestinal disinfectant.

Sprue.— Sprue is a disease of the small intestine characterized by functional motor disorders and impaired absorption of foods particularly fats (Ingelfinger in Portis[illegible]) The cause is not known but a nutritional deficiency probably resulting from a protracted diet deficient in vitamin B complex and in proteins and too rich in carbohydrates, is suspected. Manson Bahr[illegible] emphasizes the importance of preceding intestinal infection. Progressive weakness, mental depression severe macrocytic anemia, muscular wasting and emaciation are typical of fully developed cases.[illegible] In contrast to pernicious anemia the stomach usually contains free hydrochloric acid. The most important features are diarrhea with pale, greasy foul-smelling unformed watery stools, cramps and distention Secondary deficiencies develop particularly of the fat soluble vitamins. The characteristic pathologic changes are atrophy of the intestinal mucosa and extreme depletion of the fat reserves of the body Not too far advanced cases respond to liver therapy in a way similar to pernicious anemia.

The disease is common in some tropical countries, particularly India and China, but as is now known a probably identical disease is not rare in the temperate zones of Europe and America The infantile form is known as celiac disease.

[illegible] Aitken, R. The Reaction of the Stools and Its Relation to Diseases of the Skin, Brit J Dermat. 51: 12-17 1939

[illegible] Oelling, J Dermatitis Follicularis Hyperkeratotica Pruriginosa Circumscripta—Successful Treatment With Charcoal, Zbl. 33: 4[illegible], 1931

[illegible] Schwartz H J Association of Intestinal Indigestion With Various Dermatoses, Arch. Dermat & Syph 13: 673-674 1926

[illegible] Montlaur H., and Courtière, [illegible] Les modifications chimiques des selles au cours de l'évolution de l'eczéma chez le nourrisson Bull Acad. Med, Paris III, 104 [illegible] 1930

[illegible] Herrmann, E H and Bellafant J O. Ekzemfälle und Darmkrankheiten, Nederl. tijdschr geneesk 1930 I 1316-1321 Zbl 33 240

[illegible] Porges, O Ueber den Zusammenhang von Dünndarmkatarrh und Dermatosen, Wien. klin. Wchnschr 1933 I [illegible]

[illegible] Manson-Bahr P and Willoughby H. Sprue, 200 Cases, Quart. J Med. 23 11-443 1930.

[illegible] Hanes, F M Sprue in H A Christian's, Oxford Medicine Vol. 4, New York, 1930 Oxford University Press, p 63

Dermadromes—The long known[3030] importance of the mucocutaneous manifestations of the sprue syndrome has recently been re-emphasized by Kaufman and Smith[3031] Glossitis probably reflecting similar changes in the intestinal tract is very common and if combined with characteristic diarrhea is suggestive of the disease

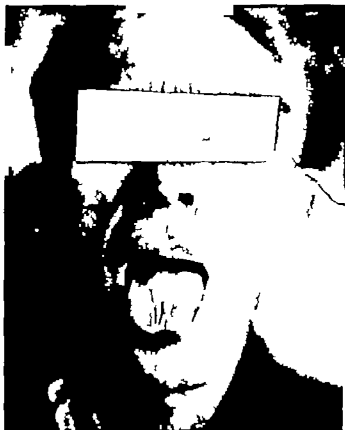


Fig 373—Sprue Atrophic glossitis and facial pigmentation. (From Manson-Bahr Sir Philip Quart. J Med)

Stomatitis and glossitis occur in more than 75 per cent of the cases,[3032,3033] often preceding anemias.[3030] The tongue changes involve at first the edges and the tip later the entire surface starting with aphthae or minute shallow ulcers along the edges[3033] and inflammation of the fungiform papillae. The sense of taste is often lost in acute sprue and salivation is increased. The glossitis may precede the diarrhea. The tongue is extremely tender especially in the presence

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[3030]Bahr P H A Report on Researches on Sprue in Ceylon, 1912-1914 London, 1915, Cambridge University Press

[3031]Kaufman, W H and Smith D C Cutaneous Changes in Sprue Syndrome, J.A.M.A. 121 168-172 1943.

[3032]Thaysen, T E. H Ten Cases of Idiopathic Steatorrhea, Quart. J Med. 4 359-366, 1935.

[3033]Low G C Sprue, 150 Cases, Quart J Med 21 523-534 1928.



Fig. 374.—Sprue. Chloasma periorale. (From Kaufman, W. H. and Smith, D. G. J. A. M. A., 1913.)

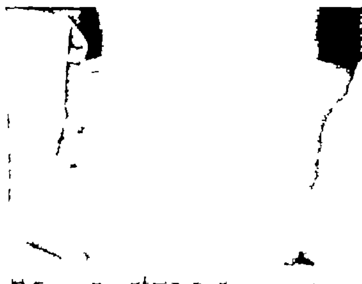


Fig. 375.—Sprue. Pigmentation of abdomen. (From Manson-Bahr, Sir Philip. Quart. J. Med.)

of aphthous ulcers. There often are indentations of the edges of the tongue caused by the teeth Atrophy of the tongue with complete disappearance of the fungiform papillae occurs later [illegible] In such cases the tongue is narrow and pointed

The fully developed picture shows absence of the filiform papillae with the fungiform papillae remaining as prominent shiny sometimes hemorrhagic points [illegible]

Painful rhagades may cut the tongue in both directions. Fissuring of the angles of the mouth is also common Buccal and infralingual aphthae have been found varying from 22 5 to 67 per cent in large series.[illegible]

The skin is pale dry flabby grayish yellow but not icteric. Large freckles and symmetric chloasma like patchy or diffuse pigmentations have been recorded Even Addison s disease is sometimes suggested. Some degree of pathologic pigmentation was seen in the majority of the well-observed cases.[illegible] Pellagroid pigmented patches on the dorsa of the hands have also been seen [illegible] The pigment was found iron free thus probably being melanin The pigmentations in sprue seem to improve with treatment[illegible] of the disease

Intestinal polyposis may be associated with jet black melanin pigmentation in dots and spots about the mouth the lips and over the hands.[illegible] Similar pigmentations have been seen in *gastrojejunocolic fistula tuberculosis of the ileum celiac disease* Jeghers[illegible] believes that pigmentation without pellagra is more pronounced in diseases of the small intestine than in disorders of the colon Urbach[19] suggests that the oxidation of phenol substances possibly also of skatol may lead to excessive melanin formation though no proof for this probability has been offered as yet

Ulcerati e Colitis.—Nonspecific ulcerative colitis is in about 2 to 3 per cent complicated by skin lesions.[illegible] Most troublesome and conspicuous are ulcerations which may occur[illegible] on the lower legs. They increase rapidly in size after taking on a kidney shape They are painful and quite deep but the healing tendency is marked The appearance and disappearance of the skin lesions may reflect the course but not the extent of the colitis.[19,illegible,2947]

The author observed a case of ulcerative colitis in a woman who after an unhappy married life went through the excitement of a divorce The periods of worry and excitement not only produced acute attacks of colitis but also new and severe ulcerations of the legs.

[2944] Bargen, J A Complications and Sequelae of Chronic Ulcerative Colitis, Ann. I t. Med 3: 335-352, 1929

[2945] Bargen, J A Presen Status f Colitis and Regional E teritis, Bull. New York Acad. Med 20: 34-35 1944

[2946] Brunsting L A Goeckerman, W H and O Leary P A Pyoderma Gangrenosum, Arch Dermat & Syph 22: 655-680 1930

[2947] Jones, C M Peripheral Complications of Ulcerative Colitis, Med Clin. North America, 16 919-938, 1933

Pigmentations of the face and body also of the dorsa of the hands may occasionally take on the characteristics of sprue or pellagra. Thickening and distal loosening of the nails may occur [illegible]



Fig 376 — Leg ulcers in ulcerative colitis (Courtesy Dr J R Jankelson)

Dryness a d scali ess follicular keratoses symmetrical atrophy pigmentations various erythemas and cheilitis have been observed and at least in part have been interpreted as a taminoses [illegible]

Tongue and buccal changes occurred in 60 per cent of Mackie s[illegible] 75 cases. They may correspond to those in sprue There was accentuation of the papillae fungiformes strawberry tongue i the earlier stages and smooth atrophy later In se ere cases a stomatitis indistinguishable from that in pellagra may de elop

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[illegible] Minter J J Pyoderma Gangrenosum, Onychocryphosis and Onycholysis With Colitis Arch Dermat & Syph 40: 841-843 1939

[illegible] Mackie T T Ulcerative Colitis II The Factor of Deficiency States, J.A.M.A. 104 173-17 1935

Whitfield[illegible] called dermatitis colonica a parapsoriasis like eruption of discrete flat red macules with telangiectases and pigmentation He connected the dermatosis with colitis and an abundance of streptococci in the stools.

Urticaria seems to be relatively common in colonic disease.[illegible] The author observed the first outbreak of psoriasis in a man of fifty in typical localization immediately after a *colostomy* had been performed because of rectal cancer The patient remained well for two years, but never recovered from his psoriasis. Pruritus without visible skin lesions has been seen in patients with colostomy stomata



Fig 377 —Colitis ulcerosa Female aged 52 years. Multiple kidney-shaped rapidly progressing and healing ulcers of the legs Remarkable parallelism of course of the severe colitis and the ulcerations. Both subject to psychogenic influence as demonstrated during the excitements of divorce proceedings. Discoloration of the skin is partly due to gentian violet (Patient of Dr Greenberg)

Treatment —If certain dermatoses are caused by pathological contents of the bowel it seems logical to try to treat such skin lesions by the cleansing of the intestinal canal with laxatives, increased intake of water and enemas. These methods are not much used today However in urticaria and pruritus, catharsis is worth while trying The use of saline cathartics seems satisfactory In spite of the good experiences of some authors[illegible] colonic irrigation has not become a generally accepted method of treatment Urticaria lichen urticatus, pruritus

[illegible] Whitfield, A On Hitherto Undescribed Diseases of the Skin, Brit J Dermat. 44 24 28 1932.

[illegible] Bockus, H L., Bank, J and Wilkinson S A Neurogenic Mucous Colitis, Am. J M. Sc. 176: 813-830 1928

[illegible] Urbach, E Das subaquale Darmbad i der Dermatologie Arch. f Dermat. u. Syph. 160: 833-840, 1930

and toxicodermas seem to be the dermatological indications for the use of this method. The technique is well described by Urbach[illegible] and by Read[illegible] Large doses of activated charcoal to absorb toxic products in the bowel may be used for the same conditions.[illegible]

The most important method of treatment consists in the proper diet for which the textbooks of gastroenterology and nutrition may be consulted. Very recently Urbach[illegible] has presented an excellent modern treatise on the dietary treatment of dermatoses including those of gastrointestinal origin

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[illegible] Read, H. S. Colonic Irrigation, Med. Physics, p. [illegible], 1944, The Year Book Publishers, Inc., Chicago.

[illegible] [illegible], J Dyspeptische Hautkrankheiten, Zbl [illegible] [illegible]

Chapter XLII

DISEASES OF THE LIVER AND PANCREAS

The Liver

The bile, the secretion of the liver, contains bile pigments, bile salts, cholesterol, lecithin and mucin.[illegible] The pigment bilirubin is a waste product from destroyed erythrocytes which have been collected by the reticulo-endothelial system. The liver takes bilirubin from the blood and secretes it into the bile. Bilirubin which has passed the liver is slightly different from blood bilirubin. This is demonstrable by the two van den Bergh reactions. Biliverdin is an oxidation product of bilirubin. The bile salts facilitate the action of the pancreas and the absorption of fatty acids. Cholesterol is a lipid of the sterol group mainly derived from animal fats. The liver supplies most of the blood sugar and forms all the urea. It synthesizes most of the fibrinogen, thus playing an important role in blood coagulation.

Liver damage may result in hemorrhagic disease with prolonged clotting time and prothrombinopenia.[illegible] The liver has a significant detoxifying function. Many metabolic and external poisons are either destroyed in the liver or excreted into the bile. Disturbance of the detoxifyi g function of the liver plays an important role in the pathogenesis of allergy. The liver is often called the second barrier against poison, the first being the intestinal wall.[illegible]

Dermadromes.—*Jaundice* may be caused by *obstruction* in the common duct or in higher parts of the bile duct system, provided the dammed up area is large enough. The bilirubin is then reabsorbed into the blood. There are many causes for such an obstruction, the most important being gallstones, neoplasms, scarring or inflammatory swelling.

In *toxic or infective jaundice* the bilirubin secretion of the liver cells is disturbed. Therefore, the blood cannot be sufficiently freed of its bilirubin, which soon reaches an icteric level. Toxic or infective jaundice is the most common form of jaundice.[illegible] It is encountered in yellow fever, Weil's disease, typhoid fever, pneumonia and other infections, in poisonings from chloroform, gold, arsenobenzol, phosphorus, carbon tetrachloride, some mushrooms, e.g. helvella, and a great variety of other toxic agents.

In *hemolytic jaundice* the rate of bilirubin production from destroyed red cells exceeds the capacity of the liver to excrete it. The urine as well as the feces retain normal color. Some forms of hemolytic icterus are hereditary.

These causes of icterus are not always sharply divided. Thus, e.g. obstruction may lead to absorption of bile but also to infection and damage to the liver

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[illegible] Urbach, E. Ueber die [illegible] Beziehungen zwischen Leber und Haut, Arch. f. Dermat. u. Syph. 175: 767-787, 1937.

cells with subsequent failure to drain bilirubin from the blood Jaundice is probably the most regularly encountered skin manifestation of any internal disorder

The color of jaundiced skin varies widely from a slightly yellow tinge to lemon greenish brown or even purplish shades. Greenish jaundice is explained by cyanosis brown or black hues come about by combination with various pigmentations. Orange or saffron color of the skin suggests intrahepatic jaundice greenish to bronze obstructive jaundice. A greenish tint may develop in intrahepatic jaundice in the presence of liver necrosis and also in the receding stage of jaundice.[illegible] Yellowish blue or green is considered almost diagnostic of a tricuspid lesion or a relative insufficiency of the valve (Wearn after Jeghers[illegible])

The distribution of jaundice is not always even In slight and early cases only the sclerotics or the hard palate may appear yellow In catarrhal icterus the discoloration usually appears on the head neck the upper trunk, the abdomen the legs and finally on the forearms and hands.[illegible] The jaundice may come on in repeated attacks, each increasing the color of already yellow areas. At the height of the icterus the areas which appeared first are then the darkest Thus the upper part of the body is generally darker than the lower part [illegible] The regression of icterus follows the reverse order of its appearance, so that sclerotics and face may still be yellow when all other parts have reached a normal color The differences in intensity are not yet sufficiently explained. Differences in concentration and in the amount of blood which during a given time, flows through and stains the areas are likely to cause difference of intensity of color

Hyperemia or urticaria causes local increase of the icterus probably because of greater capillary permeability this is easy to demonstrate under glass pressure. In subclinical icterus the hyperemic halo of a histamin reaction leaves a yellow ring after the hyperemia has disappeared With this skin test a bilirubin level of as low as 1 mg per cent can be shown.[illegible] The remaining local icterus after disappearance of urticaria factitia is called yellow dermographia.[illegible] It may be present prior to clinical icterus. Two cases of contralateral jaundice and ipsolateral edema in apoplexy and cardiac decompensation have been described by Page [illegible] It has been suggested that in these instances the edema prevented the entrance of the pigment but this is unlikely since a local edema like a wheal increases icterus.

Localized jaundice about th umbilicus due to rupture of the common bile duct was described by Ramsehoff (see Teghers) [illegible]

[illegible] Lichtman Diseases of the Liver Philadelphia, 1942 Lea & Febiger

[illegible] Kovacs, F Ueber die Verteilung des [illegible] Icterus, Wien klin Wchnschr 1928 II 1456-1457

[illegible] Umber F and Rosenberg M Regionärer Icterus, Deutsche med. Wchnschr [illegible] [illegible] 1929

[illegible] Schick, B Die Verteilung der Gelbfärbung in der Haut beim Icterus neonatorum, Ztschr f Kinderh [illegible] [illegible], 1924

[illegible] Meyerhofer E [illegible] Regel der früh [illegible] Abstufung im Verhältnis zum Hautikterus, Wien klin Wchnschr 1929 I 573-87

[illegible] Klein O Nachweis [illegible] latentem Icterus durch intradermale Histaminjnjection Klin. Wchnschr 1931 II 2032-2035

[illegible] Derbes V J and Engelhardt H T Yellow Dermographia Arch. Dermat & Syph. 48 310-311 1943

Several tests using injection of dyes into the skin have been devised to demonstrate subclinical icterus [illegible] but none has become important since accurate quantitative determinations of bilirubin in the serum are now generally made with the van den Bergh method. Intracutaneous injection of 1 per cent potassium ferricyanide produces a blue spot if the icterus is caused by an iron containing blood derivative This is known as the positive Brugsch test [illegible] Bilirubin is iron free The value of the Brugsch test for iron has recently been doubted [illegible] The extrahepatic type of icterus is seen in the presence of very numerous skin hemorrhages which may cause generalized yellow discoloration The Brugsch test is also positive in icterus neonatorum

Itching sometimes restricted to some areas is a common and troublesome though not invariable symptom of icterus. It is absent in hemolytic icterus [illegible] It is controversial whether the presence of bile salts and bilirubin is responsible for the pruritus. Insulin in doses of 20-50 units daily seems to relieve the itching [illegible] In senile and other types of pruritus sine materia tests sometimes indicate an impaired liver function [illegible]

The capillaries of icteric skin are more permeable than those in the normal skin

Urticaria is frequently seen The icteric skin develops a wheal after injection or iontophoresis of a one hundred times weaker histamin solution than is necessary to create the same effect in the normal skin [illegible] Cantharides draw blisters in a shorter time in icteric than in normal skin [illegible]

The disappearing time of an intracutaneous wheal of isotonic salt solution (McClure and Aldrich Test[illegible]) is shortened in icterus.[illegible]

Long lasting jaundice with hypercholesterolemia, as in biliary cirrhosis may produce *xanthomas* in the skin One has to look for these lesions in the creases of the finger joints and about the elbows. These xanthomas are reversible with changes in the blood cholesterin [illegible]

Liver spots are chloasma like hyperpigmentations in the face, caused by melanin deposits. They are suggestive of liver disease but are neither frequent nor specific. The French term masque biliaire is applied to a periocular chloasma hepaticum.

The *hemorrhagic tendency*[illegible] may be severe however it is not parallel to the icteric indexes [illegible] It constitutes an added risk in any surgery on a jaundiced patient *Gastrointestinal bleeding is usually the first hemorrhagic* symptom in obstructive jaundice. An alarming picture of hemorrhagic disease

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[illegible] Dadd G Sulla ricerca della bilirubina nella pelle degli itterici, Riv di clin med 32 501-506 1931

[illegible] Brugsch T Zur Analyse des Ikterus, Deutsche med Wchnschr 1939 I 657-658

[illegible] Rosenthal F Hautjucken bei Ikterus Therap d Gegenw 79 297-301 939

[illegible] Malamud, T Insulin beim Pruritus der Ikteruskranken, Prensa méd argent. 17 1234-1236, 1931 Zbl 28 484

[illegible] Hübner K Hyperbilirubinaemie Pruritus, Arch f Dermat Syph. 176 509-514 1937

[illegible] De Tullio R La permeabilità dei capillari l'indice infiammatorio della cute negli epatopazienti. Riforma med 46 241-244 1930

[illegible] Mora, J M and Jirka F J The Effect of Jaundice on Intradermally Injected Salt Solution, J Lab & Clin Med 20 719-722 1935

[illegible] Comfort M W Shepard V O and Snell A M Xanthomatous Biliary Cirrhosis, Proc Staff Met., Mayo Cl 16 374-377 1941

may follow.[illegible] Quick emphasizes the absence of petechiae and the presence of large ecchymotic areas.

The lack of vitamin K, which maintains the normal level of serum prothrombin, is now recognized as the cause of the hemorrhagic disease in obstructive jaundice with not too much damage to the liver.[illegible]

Extensive liver damage, whether primary or secondary, may account for the inability of the liver to produce prothrombin. The resulting hemorrhagic tendency is due to hypoprothrombinemia and is not relieved by vitamin K.[illegible]

Cirrhosis of the Liver.—In portal cirrhosis the skin is usually grayish or sallow. Icterus, often little pronounced, is seen in 30 to 65 per cent of the cases.[illegible] Pruritus is common. Urbach[illegible] has produced considerable evidence



Fig. 378.—Cirrhosis of the liver. Large vascular spider above the clavicle surrounded by several small spiders. (From Bean, W. B.: Medicine.)

tracing the pruritus in hepatic cirrhosis to the disturbed protein metabolism of the liver. While there are no conspicuous dermadromes, the frequent appearance of spider-like telangiectases is of theoretical and to some extent prognostic interest.

[illegible] Krach, R. R.: The Diagnosis and Treatment of the Purpuric Diseases, South. M. J. 34: [illegible] 94[illegible].

[illegible] Faris, J. D., and Thompson, F. [illegible]: 71 Cases of Cirrhosis of the Liver, Ann. Int. Med. 2[illegible]: 2[illegible]-2[illegible] 19[illegible].

[illegible] Ra[illegible], D., and Pa[illegible], J.: The Natural History of Laennec Cirrhosis of the Liver, Analysis of [illegible] Cases, Medicine 31: 2[illegible]7 2[illegible] 19[illegible]2.

PLATE VI

1 Herpes simplex seen in ma y f ers

2 Hepatic cirrhosis. Ascites, congested veins, illary lopecia, pigmented male nipple. Not bsence of striae.

3 Hepatic cirrhosis. Erythema of the palmar eminences, so-called li er palms and vascular spider in unusual location.

4 Hepatic cirrhosis. Vascular spider

5 Biliary cirrhosis. Four years after ligation of common duct, jaundice

6 Biliary cirrhosis. Bleeding gums, deca ed teeth.








PLATE VI

Vascular spiders (cutaneous arterial spiders,[3944] nevus araneus like or stellate lesions, tache stellaire étoile vasculaire) were first described in an alcoholic (hepatic cirrhosis) by Erasmus Wilson.[3945] Their physiology histology and clinical significance has recently been studied by Patek, Jr Post and Victor[3946] Bean[3944] and many other authors particularly French

The vascular spider consists of a "body" which is a central raised pin head to lentil-sized papule from which the "legs" spokes or radicles radiate. The latter are telangiectases which branch out and anastomose in many ways. An area of erythema often surrounds the central punctum and an anemic halo around the red area is occasionally visible. The color of the central eminence is bright red but does not show well in infra red photography [3944] which is one of the proofs of its arterial nature. Veins appear darker in infra red The temperature of the vascular spider is 2 3° C (3-5° F) higher than the normal skin surface. The blood flows from the center to the periphery and pulsation can usually be demonstrated if controlled glass pressure is applied The intravascular pressure, as measured by the force necessary to stop the pulsation and blanch the lesion is between 70 and 90 mm of Hg Adrenalin blanches the finer ramifications and histamine deepens the red area more than the adjacent skin The number of spiders varies from a single one to an occasional exanthem of the density of mild chicken-pox. This, however is rare. The spiders are, with few exceptions restricted to the upper half of the body with a predilection for the neck clavicular areas and face The pattern of distribution reminds of sites of benign new growths under estrogenic influence (see pregnancy and menopause) The palms are more often affected than the arms. Scattered or reticular fine telangiectases may be seen together with the spiders indicating the widespread alteration of the capillaries. Bean[3944] aptly compares this type of telangiectasis with paper money flecked with silk threads.

Besides the nevus araneus-like lesions simple telangiectases in small plaques at the costal arch were described by Galloway[3947] in various visceral conditions with stasis including cirrhosis.

Stellate telangiectases in cases of Laennec's cirrhosis, have been found in 15 per cent by Ratnoff and Patek,[3949] 56 per cent by Cirovacki (after Bean) and 75 per cent by Bean[3944] but they are also encountered in other liver diseases e.g in catarrhal jaundice in Weil's disease and in common duct stone with jaundice though decidedly less often [3944] The chronicity of the disease does not seem to have much bearing on their development since they have rarely been found in hepatic carcinomatosis. It can generally be said that the presence of spiders indicates a more severe cirrhosis [3944] Improvement of the hepatic condition may be followed by disappearance of the spiders.

The histological[3944, 3946, 3948] character of the spider is that of a coiled artery larger than that ordinarily found in the surface of the skin The arterial wall has

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[3944] Bean W B The Cutaneous Arterial Spider A Survey Medicine 24 243-331 1945.

[3945] Wilson, E Eruptive Angiomata J Cut Med & Dis Skin 2 [illegible] 1869

[3946] Patek, A J Jr Post J and Victor J The Vascular Spider Associated With Cirrhosis of the Liver Am J [illegible] 4-3 [illegible]

[3947] Galloway J Visible [illegible] of Visceral Diseases Brit M J 904 I 883-887

[3948] Wegelin Cirrhosis of the Liver With Stellate Telangiectases of the Skin, Schweiz Ztschr f Path [illegible] 8 374-387 1 2

some characteristics of the arterial segment of an arteriovenous anastomosis (glomus) The spider is decidedly different from a hemangioma

The free urinary *estrogen* values in advanced cirrhosis are high and the androgen values are low [140] The diseased liver seems unable to inactivate



Fig 379.—Hepatic cirrhosis, gynecomastia.



Fig 380 —Hepatic cirrhosis, pigmented and enlarged male nipple

estrogens[illegible] and the testicular atrophy which is common in fully developed cases, probably accounts in part for the lack of androgens. Androgens continue to be inactivated by a liver which has been damaged enough to be unable to inactivate estrogens. Thus the balance between estrogens and androgens is upset.[illegible] These endocrine disturbances help to explain the production of spiders, palmar erythema and chloasma which also occur in pregnancy and which can be provoked by administration of estrogens to cirrhotic patients.[illegible] The low level of androgens may increase the effect of the high estrogens. This may also account for the *gyne-*



Fig. 251.—Hepatic cirrhosis. Axillary alopecia, enlarged male nipple.

comastia which is frequently present in advanced cases. Paula[illegible] found gynecomastia with increase of milk ducts, cyst formation and milk secretion in 5 out of 7 autopsies.[illegible] The *nipples* are often enlarged, cylindric and erect, the areola deeply pigmented. The *loss of axillary* and to a lesser extent pubic hair[illegible] is common in cirrhosis. This symptom may also be related to endocrine disturbances, especially testicular.

[illegible] Biskind, M. S., Biskind, G. R. and Biskind, L. H.: Nutritional Deficiency in the Etiology of Menorrhagia, Metrorrhagia, Cystic Mastitis and Premenstrual Tension. II. Treatment With Vitamin B Complex. Surg., Gynec. & Obst. 78: 49-57, '44.

[illegible] Bean, W. B.: A Note on the Development of Cutaneous Arterial "Spiders" and Palmar Erythema in Persons With Liver Disease and Their Development Following the Administration of Estrogens. Am. J. M. Sc. 204: 251-253, '42.

[illegible] Bean, W. B.: Acquired Palmar Erythema and Cutaneous Vascular "Spiders." Am. Heart J. 25: 463-477, 1943.

[illegible] Paula, F.: Gynäkomastie und Leberzirrhose. Deutsches Arch. f. klin. Med. 168: 83-89, 1930.

[illegible] Martin, E.: Syndrome pileux. Gaz. Rev. méd. de la Suisse Rom. 51: 674, 1931.

Erythema of the palmar eminences (liver palms) especially of the hypothenar often associated with spiders was observed in about 25 per cent of the patients with cirrhosis[3461] but only in 4 per cent of Ratoff and Patek's[3460] 386 cases. The condition also occurs in other internal disorders e g gastrointestinal ulcer rheumatoid arthritis heart disease chronic sepsis, pulmonary tuberculosis chronic deficiency states and in pregnancy It is also occasionally seen in normal persons. Palmar erythema, like its related lesion the vascular spider may wax and wane with fluctuations in the severity of the liver disease.[3461] It has been

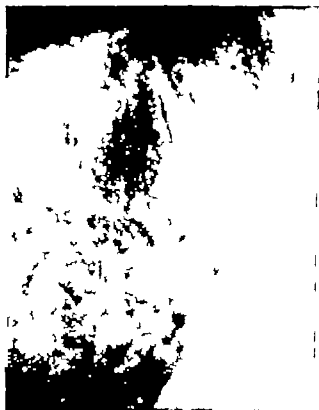


Fig 383 —Hepatic cirrhosis axillary alopecia Male aged 50 years.

shown that palmar erythema can be provoked by potent estrogens in persons having some of the mentioned diseases.[3462] The erythema is arterial in character and warm to the touch The capillaries are increased The palmar erythema is sometimes combined with erythema of the fingertips clubbing of the end phalanges and Hippocratic nails.

The well known appearance of *dilated veins* around the navel (caput medusae) is relatively rare. Congested veins are of frequent occurrence in the presence

[3461] Perera, G A A Note on Palmar Erythema (So-Called Liver Palms) J.A.M.A. 119: 1417 1942.

of ascites.[illegible] In more than 40 per cent of the cases[illegible] dilated veins in the skin of the abdominal and thoracic walls show the existence of an established collateral circulation Infra red photography may detect tortuous veins before they become visible. Edema of the ankles occurs in the majority of the cases. Hemorrhoids are seen more frequently in cirrhosis than in comparable groups (Chapman Snell and Rowntree after Ratnoff and Patek[illegible]) *Hemorrhagic* phenomena are observed in about 25 per cent of the



Fig. 3[illegible] – Biliary cirrhosis Slick tongue

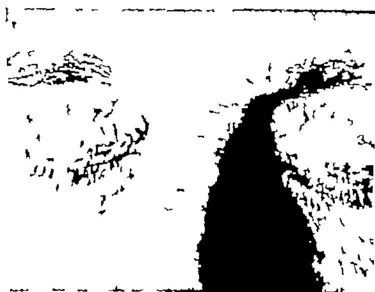


Fig. 3[illegible] Xanthoma [illegible] palpebrarum in patient [illegible] biliary cirrhosis

cases of cirrhosis. One-third of the hemorrhagic patients show purpura.[illegible] Striae are absent

In *biliary cirrhosis* the jaundice is severe Bleeding from the gums is frequently seen Xanthomas in the palmar creases the soles and elsewhere may develop in hyperlipemia [illegible]



Fig. 345.—Cachexia (biliary cirrhosis) Hippocratic nails.

Gallstones and Cholecystitis.—Little is known of skin manifestations in diseases of the gallbladder The infected gallbladder may become a focus of infection and cause cutaneous lesions.[illegible] A stone in the common duct may cause icterus with its cutaneous sequelae Xanthoma especially of the lower eyelid salivation gingivitis transient yellow or persistent chloasmatic spots on forehead and cheeks urticaria [illegible] pruritus and telangiectases are occasional manifestations of chronic cholecystitis [illegible]

The Liver in Dermatoses—Many investigators[illegible] have studied liver functions in skin diseases. This has been done with most of the liver function tests (for a practical appraisal of the liver tests see Ivy and Roth[illegible]) especially the two van den Bergh tests, the determination of urobilin and urobilinogen in the urine blood sugar tolerance tests galactose gelatine and water [illegible] phenol tetrachl rphthalein sodium [illegible] Widal s hemoplasia [illegible] Falta s bile tolerance test

[illegible] Rosterman O B and Montgomery H Disorders of Liver and Extrahepatic Biliary Ducts Associated With Cutaneous Xanthomas and Hyperlipemia, Gastroenterology 3 [illegible], 1944

[illegible] Lane C W and Stroud C M Pyoderma Gangrenosum, Arch Dermat. & Syph 27 460-468 1933

[illegible] Menagh F R Etiology and Results of Treatment in Angioneurotic Edema and Urticaria, J A M A 90 668-671 1928

[illegible] Dalsace J De quelques signes cutanés et [illegible] dans les cholecystites et les ulcères duodenaux Bull méd 1931 [illegible] Zbl 42 78

[illegible] Dubowy M Korrelation zwischen Haut und Leber Dermatologica 79 370-391 1939

[illegible] Ivy A and Roth J A Which Liver Function Test? Gastroenterology 1 [illegible], 1943

[illegible] *Dolfen H Leberfunktionsprüfungen i der Dermatologie, Arch f Dermat u. Syph.* [illegible] 495-504 1933 [illegible] 1934

[illegible] Matsunobu T Eczema and Liver Function, Eczema and Sugar Metabolism, Jap J Dermat. [illegible] 825-830 1930 Zbl 37 255

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and the determination of urobilinogen in the stools after Schmidt [2859] Other investigations were concerned with the reticulo-endothelial system of which the Kupffer cells in the liver represent an important part. The disappearance of intravenously injected congo red from the blood (Adler and Reimann test) was used as an indication of the function of the reticulo-endothelial system in the liver [2861] The reticulo-endothelial system of the skin was studied in this connection by von Leszczynski and his collaborators[2862] mostly with intracutaneous injections of histamin morphin caffein pilocarpin and trypan blue The results of the many investigations of liver function in dermatoses are not consistent. Hepatic dysfunctions were found in eczema [1662,2864-2866] acute exudative dermatoses,[2863] urticaria dermatitis after arsphenamines[2858,2861,2866] and other drug eruptions.[2867] In the larger series the patients with disturbances ranged from 10 to 40 per cent The high incidence of liver disorders in photodermatoses, drug eruptions, rosacea and other dermatoses characterized by widespread new formation of capillaries is emphasized by Milbradt[2868] and many others.

Porphyrinuria and increased fecal porphyrin which often accompany photodermatoses e.g hydroa vacciniforme, is probably the expression of a disturbed liver function [18,2869-2872] The combination of alcoholism and syphilis is apt to create the conditions which lead to hepatic cirrhosis porphyrinuria and photodermatosis. In porphyrinuria and hydroa the mechanical vulnerability of the skin may be much increased so that slight trauma may cause blisters and oozing defects.[2872,2873] Thus an epidermolysis bullosa-like picture may ensue.[2874-2876] Photodermatoses with an hepatic background and hyperporphyrinemia or porphyrinuria may also appear as xeroderma pigmentosum [2877] eczema urticaria, erythema multiforme and prurigo.

Xanthomas including the common xanthelasmas of the eyelids, should always arouse the suspicion of liver disease. Icterus is frequently found in xanthoma and even in its absence liver disorders may well be detected by function tests (Hubner after Urbach[2878])

[2865] Falchi, G Ricerchi sulla funzionalità epatica nell' eczema, Gior Ital di dermat e sif 80 704, 1937

[2866] Kordowich, F Blutbilirubinbestimmungen bei Hautkrankheiten, Arch. f Dermat. u. Syph. 176 117 122, 1937

[2867] Marquard Porphyrie im Urin bei Hauterkrankungen Zbl 53 533-570, 1936.

[2868] Milbrad W Haut und Organstörungen Leberstoffwechsel Med Welt 9 1417 1421 1935.

[2869] Carrié C Hydroa vacciniforme und Porphyrinurie Arch f Dermat Syph 163 533-543 1931

[2870] Kramer and Urbach Hydroa aestivaliforme mit Porphyrinurie Wien. med Wchnschr 1931 II 1508- 505

[2871] Brunsting, L A Brugsch, J T and O Leary P A. Porphyria Metabolism in Diseases of the Skin Arch Dermat & Syph 291 294-307 1933

[2872] Urbach, E Hydroa aestiviformis Leber und Milzcirrhose Porphyrinurie Zbl 53: 149 1936

[2873] Urbach, E and Bloch J Hydroa Vacciniforme Porphyrinopathie Hepatopathie Wien. klin Wchnschr 47 837-832, 1934

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[2876] Turner W J and Obermayer M E Porphyria With Epidermolysis Bullosa, Hypertrichosis and Melanosis Arch Dermat & Syph 37: 9-872, 1938

[2877] Hüssere bei Xeroderma pigmentosum ver pithetiomes d types divers, Bull Soc franç Derma 21 74-76 1931 Zbl 39: 542

[2878] Urbach E Beiträge zur Lichdermatosen auf Grundlage von latenter pathologischer Porphyrinbildung im Darme infolge Dysbakterie und Hepatopathie Klin Wchnschr 17 301-310 1937

Clinical experience has often shown that psoriasis, eczema urticaria[illegible] Quincke's edema rosacea and other dermatoses followed the ups and downs of liver or gallbladder disease and cleared up after their successful treatment An impressive group of such cases was presented by Smithies,[illegible] who used drainage of the duodenum mostly combined with a diet low in fat and protein and stimulation of the flow of bile by magnesium sulfate.

The opinions about associated liver disturbances in psoriasis are divergent.[illegible] The possibility of *liver damage secondary to skin disease* must be recognized This is based on observations in burns and in the experimental croton oil dermatitis of rabbits.[illegible] Dubowy[illegible] found hepatic dysfunction regularly connected with a disturbed RES of the skin.

Liver extract has been found a useful adjunct in the treatment of many skin diseases[illegible] Exfoliative dermatitis due to arsphenamine is an example.

The Pancreas

The pancreatic juice neutralizes the gastric acidity splits proteins down to amino acids (trypsin) fats into glycerine and fatty acids (lipase) and converts starches into sugar (amylase). The best known hormone of the pancreas is insulin which helps to burn sugar stimulates the formation of glycogen in the liver and muscles and probably inhibits glucose formation from amino-acids in the liver[illegible] In pancreatectomized dogs the liver becomes fatty This can be prevented by an alcoholic extract of pancreas Dragstedt's lipocaic.[illegible]

Kallikrein (padutin) is a pancreatic hormone with a vasodilating effect. It can to some degree neutralize the effect of adrenalin The most important skin manifestations of pancreatic disorders are those occurring in *diabetes* (see chapter on diabetes) Our knowledge of other pancreatic dermadromes is scanty

Dermadromes of Pancreatic Diseases.—Chronic pancreatitis and other benign disorders may provoke urticaria[illegible] eczema pruritus ani[illegible] and other nonspecific dermatoses The disturbance of fat digestion has been related to some cases of eczema[illegible] especially in infants.[illegible] The administration of pancreatic substance by mouth has been recommended

Acute necrosis of the pancreas (acute pancreatitis) is occasionally accompanied by deeply cyanotic livedo-like or spotty venous patterns (Walzel after Moynihan[illegible]) covering the abdomen chest and thighs[illegible] A palm-sized dirty

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Rueda, P Eczémas et séborrhées d ... nourrissons, Semana méd 30: 81-90 1923 Ibid 131 263

Moynihan B Acute Pancreatitis Ann Surg 81 132- 42, 1935

Walzel P Symptom der flecken-und gitterförmigen Cyanose bei acuter Pankreasnekrose, Wien. klin. Wchnschr 40 318-319 1927

gray-green slightly raised discoloration has been observed around the navel or in the lumbar area, probably caused by direct leakage and autodigestion This is known as *Turner's sign* [illegible] The abdominal cyanosis is not seen in the majority of the cases.[illegible] It is considered a pathognomonic sign.

Cancer of the head of the pancreas causes intense obstructive sometimes blackish jaundice (ictère noir) [illegible] In 56 per cent of the autopsied cases of cancer of the body or tail of the pancreas, at least one thrombosis was found.[illegible] In about one-third of the cases the venous thromboses were widely disseminated. Usually there was no jaundice present. Thromboses of veins in both lower legs with acute cutaneous inflammation may be the presenting symptom of carcinoma of the pancreatic body [illegible] No mention of thromboses is made in a recent review of 52 cases of pancreatic carcinoma.[illegible] The thromboses may affect any of the great veins of the body The neoplasms were all of the mucinous type

Pancreatic extracts, especially lipocaic and depropanex have given encouraging though not striking results in psoriasis.[illegible]

The insulin free pancreatic extract padutin or kallikrein [illegible] and similar preparations[illegible] has been used in Raynaud's disease acrocyanosis and related peripheral vascular disorders. It has also given some results in scleroderma[illegible] of the morphea type.

[illegible] Zaaijer J H. Hautverfärbung bei akuter Pankreasnekrose, Zbl f. Chir 63: 250-251 1936.

[illegible] Turner G Local Discoloration of the Abdominal Wall as Sign of Acute Pancreatitis, Brit. J Surg. 7: 394-395 1919-1920

[illegible] Langston, R S. Acute Pancreatitis. 90 Cases, Ann Surg 116 367-373, 1942.

[illegible] Sproul, E E Carcinoma and Venous Thrombosis, Am J Cancer 31 566-585, 1938

[illegible] Kenney W E. Carcinoma in Body and Tail of Pancreas With Multiple Venous Thrombi, Surgery 14: 600-609 1943

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[illegible] Downing J G Gleichen, E A and Messina, S J Deproteinized Pancreatic Extract in Treatment of Psoriasis, Arch Dermat & Syph 46 1128-1137 1942

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Chapter XLIII

DISORDERS OF THE RESPIRATORY TRACT*

Generally the *incidence* of dermatoses in very large numbers of institutionalized pulmonary patients was below the average of the general population.[191] This seems to be due to the sheltered life and the absence of occupational hazards.

Cyanosis is marked in many respiratory diseases. The blue discoloration may be of short duration as for example in the whooping cough attack or it may be longer as in diphtheria some cases of pneumonia pleuritis emphysema or large mediastinal tumors.

The frequency of *acrocyanosis* and erythrocyanosis in a series of about 5000 cases of pulmonary tuberculosis is emphasized by Szanto.[43,3497] Papulonecrotic and indurative tuberculous lesions have been described in connection with acrocyanosis[3498,3499] and livedo racemosa. Women are particularly subject to acrocyanotic conditions which may account for the female dominance in tuberculosis indurativa (erythema induratum).

Telangiectases on the thorax are said to occur in 45 per cent of patients with pulmonary tuberculosis. They are called *Francke's striae* a misnomer since they are actually telangiectases and not atrophies.[50, 43,3,50]

These telangiectases are at most 1 cm. long straight curved or branched thin sharply drawn blood vessels in the skin over the upper dorsal vertebrae and along the costal arch in front of the anterior axillary line. The latter are much more common in men (11 per cent) the former about equally frequent (3 per cent) in both sexes.[43] Francke's striae seem to be independent of the severity of the lung process but more apt to occur in cases of long duration. They are probably due to lung and pleural involvement adjacent to or underlying the respective skin areas. The telangiectases are not characteristic of tuberculosis since they are encountered in normal persons and also in emphysema. They are common in elderly men.

Sorgo[3500] found the *skin over parietal pleuritic lesions* thicker and slightly edematous. It is consistent with this observation that hypodermic injections of 1 per cent solution of congo red into symmetric sites of the thorax showed in 36 out of one hundred patients with pulmonary tuberculosis a larger spot on the diseased side.[3500]

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*This chapter includes the nonspecific dermadromes of pulmonary tuberculosis.

[3497] Szantó J.: Hat verändertes [illegible] bei Lungentuberkulose, Dermat. Wchnschr. 1939 II 1190-1008.

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[3500] [illegible] L.: [illegible] aberrolatici, Riv. di pat. [illegible] d. tuberc. 4 403-414, 1930

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Striae thoracicae in lung disease have been discussed under the heading striae.

A rapid course in pulmonary tuberculosis often increases the *succulence* of the skin. In chronic cases the skin is more apt to be thin and dry—even diffusely atrophic resembling senile skin. Szantó[illegible] considers these changes as nonspecific and inherent to the severe disease.

Fungous diseases are frequent. Pityriasis versicolor once considered a characteristic accompaniment of pulmonary tuberculosis, has become relatively rare 1.5 per cent.[illegible] This is probably due to better bathing conditions. However it is still three times more frequent among the dermatoses of the inmates of lung sanitariums than among the dermatoses of nontuberculous groups. The incidence of epidermophytosis is 6 times greater,[illegible] sweating probably being a factor.

Many statistics emphasize the high incidence of *acne* among the patients of lung sanitariums. The percentages range from 7 per cent[illegible] over 12 per cent[illegible] to about 40 per cent.[illegible] However these statistics lack comparable controls in the corresponding age classes of the healthy population. Overeating of fats during dietetic treatment may be responsible. The more severe acne dorsalis is often found over the site of the greatest pulmonary involvement.[illegible] Szantó[illegible] in his very large series confirms the relatively great frequency, severity and incidence in age groups up to 40 and 50 years. Exacerbation of acne after artificial pneumothorax has been observed by several authors.[illegible] Shoji[illegible] found the eyelashes of patients with pulmonary tuberculosis to be longer than those of normal controls. Chloasma was found twelve times more frequently than in the general population.

Since it had been suspected that pulmonary tuberculosis in *red-haired* persons takes a more rapidly fatal course, Bogen[illegible] compared a group of red haired persons with the average of 10 000 other patients with pulmonary tuberculosis. No significant differences in the fatality rate could be found.

The pressure in the *skin capillaries* was found higher in fibrotic pulmonary tuberculosis than in exudative forms.[illegible] In a series of 241 cases of pulmonary tuberculosis, the capillaries of the nailbeds of the fingers on the side of the more active lung lesion were found more dilated than on the other side. The side of gross fibrosis and caverns is often marked by deformed capillaries on an anemic background.[illegible]

Bronchial asthma is sometimes combined with eczema of the flexor surfaces. Alternating between eczema and asthma also familial accumulations of both

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[illegible] Kriest, K. Lungentuberkulose in Verbindung mit anderen Erkrankungen, Leipzig, 1937 Georg Thieme

[illegible] Shoji, A. Ueber die langen Cilien bei Phthisikern, Acta soc. Ophthalm. Jap. 35 478-483, 1931; Zbl 40 61

[illegible] Bogen E. Red Hair and Tuberculosis, Am. Rev. Tuberc. 43 [illegible]-347 1941

[illegible] Sahurov M. Y. Hautgefässdruck bei Lungentuberkulose Ztschr f. Tuberk. 66 [illegible]-144 1932

[illegible] Stefko, W. and Glagolewa M. Untersuchungen am Capillarnetz bei Tuberkulose im Zusammenhang mit den klinischen [illegible] Angaben, Beitr. z. Klin. d. Tuberk. 73 641-656, 1930

conditions is well known The discussion of these relations belongs to the province of allergy

The lunulae of the *fingernails* were found absent from all fingernails five times more frequently in patients with pulmonary tuberculosis than in controls and eleven times more often when the tuberculosis was complicated by silicosis.[1144] Heller considers the disappearance of the lunulae an important diagnostic and prognostic sign but it is not rarely seen in healthy person

Clubbing of the fingertips often accompanies chronic pulmonary lesions e g emphysema pulmonary abscess bronchiectasis and carcinoma [844] Clubbing occurs in 17 per cent of cases of chronic pulmonary tuberculosis. It seems more



Fig 186 —Clubbed fingers, bronchiectasis

common in Negr males than in whites and it indicates a poor prognosis. [69] The terminal phalanges become thicker and the nails larger and curved in both the k ngitud nal and transverse directions

Pitting f the nails was observed in 100 per cent of a g up of patients suffer ng f m active pulmonary tuberculosis as compa ed with 6 per cent of a group f patient whose disease had been inactive for a relatively short period It was compl tely *absent n patients who* were inactive for longer than one yea [841]

F equent dermad mes f pulmonary tuberculosis are *thickening f the nail plate and l ng tud nal arring* The latte is known a the *Hippocratic nail* because H ppocrat s knew and described the curved nail and its ominous prog n stic sign ficanc M de n bservations[444, 18] have amply confirmed the high

[844]Banyai A L and adden A T Tuberculosis Changes in Fingernails. Arch f Dermat a. Syph 48 806-809 43

[808]Kaplan B H ad M nson L Clubbed Fingers in Pulmonary Tuberculosis Am. Rev Tuberc 44 430-440 1

[841]Hahn, A O hange in he Finger Nails in Pulmonary T berculosis Am Rev Tuberc. 20 676-691 930

incidence (76 per cent[2119]) of Hippocratic curvature in active cases. Szantó[743] however found only 5.6 per cent among 27,540 patients.

Cyanosis of the distal end of the fingernail bed was noted in 66 per cent of Hahn's group and in 4.2 per cent of Szantó's group of active cases. Differences in the severity of the cases of pulmonary tuberculosis seem to explain the great discrepancy. The cyanosis of the nailbeds is more pronounced in rapidly advancing cases. Ridging, transverse and longitudinal, does not seem to be of prognostic importance.[744]

	PRURITUS	MISCELLANEOUS
	Scarlet [illegible] desquama-tion	Mottling of extremities, [illegible] al, edema, rarely erythema [illegible]. Creases hemorrhagic, do not blanch on pressure; (Pastia's sign) elbows, knees
	Toxic Eryt[illegible] Infect[illegible] thema	
	Measles [illegible] at erup-tion. Always at desquamation	

TABLE II. DIFFUSE PIGMENTATIONS

CAUSE	DISTRIBUTION	COLOR	MUCOSAE	ASSOCIATED SYMPTOMS	BLOOD	URINE	PIGMENT	HISTORY COURSE	MISCELLANEOUS
Addison Disease	U[illegible] emphasis in normally pigmented [illegible]reas, f[illegible]ce [illegible]k, hands. Palms, nail beds, light, creases dark	Gray—tan	Slate spots common	Asthenia, hypotension, dehydration, effect of NaCl and cortin, thin skin	Hypoglycemia Low NaCl	High NaCl	Melanin in basal layer of epidermis, also in cutis (melanophores)	Chronic [illegible]th acute attacks	TB. in 90% scars pigmented, loss of pubic and axillary hair. Depigmentation rare; great variability
Exophthalmic Goiter	Addisonian type or chloasma	All degrees	Rare	Vitiligo about 10%					
Malaria	Addisonian type	Gray-tan	Rare	Splenomegaly anemia	Plasmodia?				Melanoderma in 15% mostly mild
Tuberculosis	Nipples, axillae, chloasma. Also Addisonian type	Brown	Rare	Cachexia					Rare
Pernicious and other anemias Also Sprue, Pellagra	Addisonian type diffuse in a few per cent	All shades to deep bronzing	Rare	In sprue also patches and small papules, spots besides generalized melanoderma			Melanin and iron containing pigment	Pigmentation exaggerated by exposure t[illegible] sun	
[illegible]agabonds' Disease	Uneven, patchy back, belt, covered areas more involved than hands or arms	Gray	Occasionally slate spots on buccal mucosa and tongue	Slightly lowered or normal blood pressure. Streaky depigmented excoriations. Thick skin. Pediculosis		Albuminuria common		Vagrancy, neglect. Melanoderma heals quickly under hospital care	
	All areas [illegible]hich are able to form increased pigmentation, esp. face (chloasma), linea alba, vulva, areola mammae						Melanin		Common. Diffuse and severe melanoderma rare

Stilbestrol medication in menarche									
Ovarian Tumors	Similar as in pregnancy								Mild
Ovarian Deficiency	Same				Depression				
Hepatic Cirrhosis	Some tendency in pigmentogenic areas (nipples, etc.)								Common
Cushing Syndrome	1 General, Addisonian type is inconstant 2 Face 3 Lower legs, frequent, hemorrhage	Dusky copper		Obesity striae, diabetes, etc.			Melanin except for hemosiderin in hemorrhagic lesions		Rare
Vitamin A Deficiency	Diffuse	Dull slate	Conjunctivae, esp. upper half	Phrynoderma, night blindness, keratomalacia					Rare
Scurvy (Vit. C)	Diffuse	Generally mild pigmentation					Melanin and hemosiderin	Disappears on treatment with vitamin C	Rare
Hemochromatosis (Bronzed diabetes)	Face genitals, also large covered areas of trunk.	Bronze, slate often metallic sheen	About 20% has spots, otherwise mostly free	Diabetes mellitus. Hepatic cirrhosis. Atrophy of testes. Alopecia axillaris and pubica			Melanin and Fe containing pigm.		Rare
Ochronosis	Cartilages of ears, nose, tendons of musculi recti oculorum show as triangular bluish spots in interpalpebral fissures	Gray slate-black	Very rare	Green to black cerumen		Dark or darkening on air		Prolonged absorption of phenol may cause ochronosis	Rare
Acanthosis Nigricans	Axillary, inguinal, neck, umbilicus, lips, vulva	Gray-black. Rarely non-pigmented	Papillary or granulated appearance of oral mucosa	Visceral cancer in older persons, frequently internal (endocrine) cause, e.g., obesity, diabetes in juveniles			Engrossed papillae. Melanin in basal layer		Rare

TABLE II DIFFUSE PIGMENTATIONS—Continued

CAUSE	DISTRIBUTION	COLOR	MUCOSAE	ASSOCIATED SYMPTOMS	BLOOD	URINE	PIGMENT	HISTORY COURSE	MISCELLANEOUS
Melanosis	Face, hands	Bluish-black (very rare)							Severe cases extremely rare. Slight melanoderma not rare
Hodgkin's Disease	Addisonian type			Lymphomas			Melanin		In 10% of the cases
Chronic Circulatory Decompensation	Extremities, dorsa of hands	Brown		Cyanosis, symptoms from deficiencies of the cardiac valves and decompensation			Hemosiderin		Pronounced cases rare, sl. cases common, esp. in children
Katatonic Schizophrenia and other Psychoses	Addisonian type. Sometimes quite dark			Occasional parallelism of pigmentation with course of psychoses					Pronounced cases are rare
Racial	Evenly over body	All shades	Spots, diffuse or punctate oral and conjunctival pigmentations common in all races inclined to pigmentation (Mulattoes, Mediterraneans, Jews, Arabs, Japanese, *etc.*)				Melanin	Ascendency	
Arsenic, Arsphenamine	*Diffuse or in small spots* round dis-depigmentation, "raindrops." Tru k, p [illegible] points, covered parts generally but not always, more affected	Gray-brown	Usually free	Keratoses, polyneuritis, etc.		As	Melanin, not As	Insidious onset. May or may not disappear after discontinuation of As	Fowler's solution. Drinking water. Paints. Severe melanoderma may *follow* exfoliative dermatitis from arsphenamine

Chrysiasis (Gold Deposits)	Face, neck, hands	Slate blue	Conjunctiva bulbi in inter palpebral fissure. Oral mucosa		Metallic gold (blue-black) in lower cutis and RES	Treatment of tuberculosis with gold salts. Melanoderma is prominent	
Melanosis after Gold Treatment	Corresponds to arsenical melanosis				Melanin in upper cutis	Often after rash, reversible	
Argyria (Silver Deposits)	Light-exposed areas more pronounced	Slate-bluish-black	Conjunctivae inner canthus, gums, palate	General health not affected	Silver particles in upper cutis, sweat glands, vascular walls	Occupational, treatment with silver salts	Biopsy: slit lamp not rare
Lead Poisoning	No skin pigmentation		Blue line of gums		Lead sulphide	Mostly occupational	
Bismuth	Diffuse like argyria, rare	Black-bluish	Blue gum line is common, more extensive black discoloration of mucosa rare		Bismuth sulphide	Mostly antisyphilitic treatment	
Mercury	Diffuse or Reticular		Stomatitis may be healed at time of melanoderma	Following rash. Rare. Corresponds to As melanosis		Antisyphilitic treatment, occupational	
Gaucher Disease	Diffuse mostly face hands. Also patchy, [illegible]	Ochre	Wedge-shaped pinguecula on both sides of cornea in inter palpebral fissure	Splenohepatomegaly symmetric pigmentation of the legs	Lipidosis, Hemosiderin and iron-free pigment	Chronic	Quite rare

TABLE III. DIFFUSE YELLOW PIGMENTATIONS

(Some data from Jeghers, New England J. Med., 1944)

CAUSE	DISTRIBUTION	COLOR	MUCOSAE	ASSOCIATED SYMPTOMS	BLOOD	URINE	LABORATORY TESTS	HISTORY COURSE	MISCELLANEOUS
Liver Disease	1 Icterus, diffuse 2 Chloasma, localized	Yellow-green, brown Brown spots often periocular mask like not obligatory but relatively common	Sclerae yellow	Liver disease, pruritus	Serum yellow	Dark	Icteric index higher than 5	Depends on liver trouble	
Carotinemia	Palmae, plantae, also nasi, ears, also diffuse	Light yellow	Sclerae white		Serum contains carotene	Pale, contains carotene	Carotene in serum or urine	Diabetes. History of vegetarian diet, esp. carrots, squash, etc.	Rule out icterus
Atabrin	Diffuse, mostly on dorsa of hands and feet, face, forehead. Exposed parts	Yellow	Sclerae white. Bluish discolored palate. Epiglottis, trachea (occasionally)		Normal	Pale		Malaria prophylaxis or treatment	In contrast to carotinemia, palms less yellow than dorsa of the hands
Myxedema Male Castrate	Resembling carotinemia, to which this yellow discoloration is probably due	"Old ivory." Pale yellow				Pale	Carotene may be increased in serum and urine		
Simmonds' Disease		Waxy pale yellowish		Cachexia					
Uremia	Face, hands	Pale yellow-brown				Pale	Urinary chromogen, possibly increased by carotene		
Dinitrophenol	Entire skin	Pale yellow	Sclerae yellow		Serum yellow	Pale		Reducing of weight	
Picric Acid	Entire skin	Yellow	Sclerae yellow	Vomiting, diarrhea		Normal to orange		Oral ingestion or from picric acid salve	

TABLE IV HIRSUTISM (Hypertrichosis)

	AGE	SEX	ONSET	HAIR ... ICTIONS	ASSOCIATED SYMPTOMS	LABORATORY TESTS	TREATMENT MISCELLANEOUS
Hypertrichosis without demonstrable endocrine ... ler (... pathic)	Ad lt	Both	Puberty	Face chin, pper (p, breasts, abdomen legs	None. Menstruation normal		Common Female patients embarrassed often depressed. P ychotherapy bleaching shaving etc. Electrolysis, diathermy epilation
			Menopause	Bristles bout chin			
Idiopathic hirsutism with ... stigmas, esp sec ondary ... la leficiency	Ad lt	Female	Aft p eg y t th times	Often male distribution of pubic hair f ce body hair	Menstrual disorders Abortion Sterility Obesity Hot fla hes. Diabetes. Acromegaloid features	Urinary prola too high too low or normal Hyperglycemia. Endometrial biopsy hortly before menses show absence of progestational changes. Study of aginal smears after Papanicola nd Schorr	Less common. Treatment with estrogenic hormones
Primary ovarian deficiency	Adult	Femal		Axillary nd pubic hair scant	Breasts underdeveloped long (eunuchoid) extremities. Amenorrhea sterility In f tile genitals. N libido	Excessive urinary prola	Rare
Pregnancy		Female		Increased lanugo som t mes o h ks. Rarely conspicuous	Other signs of pregnancy		
Adrenal cortical h perfunction (h pe pl l plasia)	Any ages in l ll g earl ch ldhood	Both		Face, arms legs, breasts, greater nal area male di t b ti Eyelashes. Effluvium capil lit. Male type resembling baldness	Hyperpigmentation. Precocious puberty Obesity Diabetes. Cushing syndrome	Increased androgens (17—keto-sterоid)	Rather rare

T BLE V. THE SKIN IN REL TI N TO AGE

AGE	MICROSCOPIC, ETC.	MACROSCOPIC, ETC. WRINKLES AND FOLDS	HAIR	MISCELLANEOUS
New born	Hyperemia. Corneum thin. Cells stai w ll throughout epidermis. Corium rich in cells	Hemorrhagic tendency. Vaginal bleed ng. ctivity of breasts, agnal epithel changes. Pigmented linea alba. Telangiectat tendency esp in gl ls. Hypertrophy of gums and other sympt due t estrogenic maternal nfluence. Crookedness of nails		Lack of llergic reactivity. Sebaceous and swe t glands little active
12 13 14 15 16	Apocrine glands activ. Elastica mimica devlops		Female illary hair precedes menarche. Differentiation of sex characters. Shavi g becomes necessary male	Comedones. Acne. M narche
20	Elastica mimica peak			
25		Forehead, nasolabial folds		Veins on dorsa of hands
30		Crow feet t lateral ngles of the eyes	Peak of hair growth of beard, chest, arms, hands. Occipital hairline becomes less sharp. Graying t temples	
35		Preauricular rinkles incre si g length and umber		
40	Thinning of epiderm n spit of local keratotic tendency. Reduction of stratum gran losum nd spinosum. Reduction of cutis	Cervical fold isible lateral light		All senile hanges more marked in skin exposed t light (face, dorsa ma num)
45	Decreasi g umber of mitoses in basal layer. Papilla flatten. Collagen fibers thinner. Elastica changes start i the early forties	Suborbital. Cervical folds. Lips become thinner	Male bush eyebrow or single long hairs. Female, hypertrichosis of chi	Hyperkeratoses, small h mangiom s come on gr dually

50	Reduction of sebaceous glands. Atroph of arrector muscles	Bridge of nose, ear lobe, chin, *hands*	Graying marked	Menopausal changes
55	*Water* content lowered. *Capil-la y* reactivit slower. De-creased *sensibility* to touch, pa n, emperature	Cutis hombodalis nuchae. Wrinkles of nose, ear ch n, hands, cervical folds, now marked		Hyperpigmented spots. Dryness. Teeth appear longer
60	Elastica alterations marked	Radial rinkles around mouth cheeks droopy	Pubic hair i male less curl	Purpura senilis. Penile skin rukled, darker Scrotum longer flaccid
65			Hair growth i ear ducts, nos-trils, nape, esp. in male, more conspicuous	*Atrophy* of vulva. Arcus senilis cor neae. F t hips, thi limbs, esp. in female
70		F cial ri kles crossing Fold lifted from hand returns slowly	Head hair often thin or bsent	Hyperpigment tions, keratoses, etc., umerous
75		Lips th vermilion disappears Mouth longer sunken Wrinkl g of back f hands ery marked		N il growth reduced. Toenail often thickened or deformed
80		Droop pper lid Radial circumoral wrinkles conspicuous, cervical folds ery marked. Ears larger longer flabby shapeless Nose seems longer		Tired look. Bony hand

TABLE VI. HEMORRHAGIC DISEASES
Compiled After Quick, Haden and Other Sources

	SYMPTOMS, SKIN DERMADROMES	FUNDAMENTAL DEFECT	PLATELETS (NORMAL COUNT 250-500,000)	COAGULATION TIME LEE-WHITE NORMAL 5-8 MIN.	CLOT RETRACTION TIME. NORMAL 30-60 MIN.	TOURNIQUET TEST (CAPILLARY RESISTANCE)	BLEEDING TIME NORMAL 1-3 MIN.	MISCELLANEOUS
Hemophilia	Dangerous bleeding from trauma, abrasions, etc. Bruises easily. Ecchymoses. Hemarthrosis	Hereditary failure of platelets to disintegrate and to release thromboplastin	Normal	Prolonged	Normal	Negative	Normal	Male patients. Female conductor. Very rare. Bleeding after injury delayed
Pseudohemophilia	Same as hemophilia but milder	Hereditary failure of capillaries to contract after injury	Normal or high	Normal	Normal	Negative or slightly positive	Prolonged	Both sexes affected. Rare
Hereditary (familial) Purpura Simplex	Spontan. ecchymoses or just bruises easily		Normal	Normal	Normal	Positive	Normal	Common
Afibrinogenemia (pseudo-hemophilia of the German lit.)	Like hemophilia, ecchymoses	Lack of fibrinogen prob. inherited		Prolonged. Blood incoagulable			Normal	Extremely rare
Osler Disease. Hereditary Hemorrhagic Telangiectasia	Increasing number of telangiectases which bleed easily. Cheeks, lips, ears, tongue. Dangerous recurrent epistaxes	Hereditary capillary defect	Normal	Normal	Normal	Negative	Normal	Both sexes, secondary anemia. Hepatosplenomegaly in advanced cases
Thrombocytopenic Purpura. Werlhof Disease	Crops of petechiae and ecchymoses over whole body. Severe mucosal bleeding. Severe hemorrhages from wounds. Bruises easily (skin). Urticarial character of fresh lesions. Mucosal bleeding severe	Failure of megakaryocytes in bone marrow to furnish enough platelets. Depressing influence of spleen	Low	Normal	Absent	Positive	Prolonged	Effect of splenectomy. Intradermal moccasin snake venom, 0.1 C.C. of dilution 1/3000 elicits hemorrhagic reaction
Nonthrombocytopenic or Anaphylactoid Purpura. Schönlein Purpura	Urticarial component of purpura. Petechiae in urticarial lesions which appear in crops, esp. over legs, face, bends of large joints, palms, soles often free	Allergy infection	Normal	Normal	Normal	Mostly positive	Normal	Articular swelling common (purp. rheumatica)
Henoch's Purpura	Similar to Schönlein but severe gastrointestinal symptoms	Allergy infection	Normal	Normal	Normal			
Purpura Fulminans	Hyperacute suffusions covering large areas		Normal	Normal	Normal		Normal	Mostly fatal. Very rare
Waterhouse-Friderichsen Syndrome	Hyperacute petechiae and ecchymoses, coalescent to large areas	Massive adrenal hemorrhage. Meningococcic infection in most cases	Low	Normal			Normal	Fatal. Rare. Mostly small children

TABLE VII PRURITUS

Itching, localized or generalized, pontaneous or on slight provocation like exertion, change of temperature, etc., without noticeable ski changes except such as are due to scratching ("Prurit sine materia")

I *Rule out Ped culosis capiti pubis scabies*

Itching I scabies is not alw y localized t visible lesions. Burrows may be ery inconspicuous. Urticarial lesions may have vanished. Consider allergy t plants, paints, wool, silk, external medicaments, soaps cleansers, cosmetics, flowers, occupational contact allergens, insecticides, fertilizers, garden sprays, etc.

II *Endogenous prurit*

Diabetes. If urinary sugar negative, do blood sugar test If fast ng lue below 120 mg %, glucose tolerance test necessary

Gout. Hyperuricemia. Attacks of arthritis Tophi

Subcli cal J dice. V den Bergh test. Icterus ndex. Gall bladder

U ry Disease. Kidneys. Uremia. Hypertrophy of prostate. Urethral stricture

Arteriosclerosis. Senile pruritus

Hypertension esp sudden increase of blood pressure

Gastrointesti al d sease. Hypacidity constipation diarrhea, typhlitis. Helminthes

Lymphoblastoma. Leukemia, Hodgkin disease. Mycosis fungoides before eruptions

Anemia

Visceral cancer

Focal infection Teeth tonsils, prostate, gall bladder

Drugs. Morphine, barbiturates, arsenicals, laxatives, balsamics sulfa-drugs, gold bismuth I jections, cocaine, tropi etc

Foods Seafood strawberry wheat chocolate vanilla, mustard and other condiments, etc. Too much coffee drinking

Endocr e. Pregnancy Dysmenorrhea Menopause Hyperthyroidism

Neurogenic. Preced ng herpes zoster cerebral disease e. g pruritus of the nose I brain tumor T bes

Psychogenic. Parasitophobia Pruritus after scabies. Cases of lice or scabies in surroundings. Truly psychogenic cases of pruritus are rare

Infections Syphilis (rare) Malaria chronica

Weather Humid, warm weather change of weather

Treatment

1 Treat cause if possible.
2 1 2% phenol zinc—shake lotion.
3 Epsom salt nd other saline laxatives
4 Ergotamine tartrate (gynergen)—0.5—1 mg daily over hort periods only Barbiturates
5 Autohemotherapy foreign protein.
6 Diet Vegetarian diet—no red meats, no seafood much ater (Klingery 1944) 3-5 da s on tea, toast sugar milk, butter pple only
7 Starch bath (1 handful of cornstarch t warm bath)
8 Ultraviolet light in suberythema doses.
9 Bloodletting (120-300) in hypertension.
10. Try benadryl and other ant histaminic drugs.

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